Synthesis and evaluation of narciclasine analogues

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Synthesis and Evaluation of Narciclasine Analogues

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This research has been carried out under the supervision of Dr Lorenzo Caggiano

Signed.....

Date.....

ABSTRACT

Narciclasine was isolated from the common daffodil in 1967 and was shown to exhibit potent and selective anti-cancer activity. However, current synthetic routes are generally long and low yielding, hampering its progress as a clinical candidate. This project aims to synthesise bioactive analogues using a short, elegant and scalable synthesis.

A one-pot procedure has been developed whereby a carboxylic acid is converted to an isocyanate using a modified Curtius rearrangement, which is then captured by a tethered electron-rich aromatic ring in a Lewis-acid mediated intramolecular Friedel-Crafts acylation. This methodology was then applied to produce a series of dihydroisoquinolinones as simplified AB-ring analogues in 73-90 % yields. Interestingly, the cyclisation of 3,4,5-(trimethoxyphenyl)propionic acid proceeds with selective demethylation at the 8-position when $BF_3 \cdot OEt_2$ is employed as the Lewis acid. To mimic the sp^2 centre at the 10b position of narciclasine, the analogues were oxidised using palladium on activated carbon in 39-89 % yields.

This synthetic methodology has been applied to the synthesis of the more complex ABC-ring analogues. Acetophenones were readily converted to β-ketoesters, which were then condensed with methyl vinyl ketone using a Robinson annulation reaction to generate modified Hagemann's esters**.** Reduction followed by saponification of this ester provided the corresponding acid for cyclisation using the Curtius rearrangement and Friedel-Crafts acylation. Three analogues have been synthesised using this approach in 6 steps and overall yields of 10-18 %.

These analogues have been evaluated against HT29 colon cancer cell lines, showing a range of activities from 715 μM to 15 μM, with patterns in the structure-activity relationship that mirror those in the natural products.

The prenyl and chroman groups are medicinally important functional groups found in a number of natural products. During our investigations, a mild method of prenylating an aromatic ring using $Bi(OTf)_3$ as a catalyst was discovered. The procedure was optimised and applied to a range of aryl rings to identify the scope and limitations of the reaction. It was also found that applying the same procedure to phenols gave chromans as the products. This reaction was applied to the synthesis of the natural product 2-(3-methyl-2-butenyl)-3,4,5-trimethoxyphenol, in 34 % overall yield.

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PUBLICATIONS AND PRESENTATIONS

PUBLICATIONS

Judd, K. E.; Mahon, M. F.; Caggiano, L., Efficient Synthesis of Tetrahydro-β-carbolin-1-one and Dihydroisoquinolin-1-one Derivatives as Versatile Intermediates. *Synthesis*, **2009**, 2809-2817.

ORAL PRESENTATIONS

22nd April 2010: "From Daffodils to Drugs: Synthesis and Evaluation of Narciclasine Analogues" - Oral presentation at RSC Bioorganic Group Postgraduate Symposium

POSTER PRESENTATIONS

Sept 2009: "Approaches Toward the Synthesis of Pancratistatin Analogues" – poster presentation at The XVIIIth meeting of the "Groupement des Pharmacochimistes de l'Arc Atlantique" (GP2A).

Jan 2009: "New applications of robust chemistry in the synthesis of tetrahydroisoquinolines and dihydroisoquinolones" - Poster presentation at RSC Organic Division Regional Meeting, South of England. I also presented with another group member on behalf of our supervisor in an adjoining lecture theatre.

Sept 2008: "New applications of robust chemistry in the synthesis of tetrahydroisoquinolines and dihydroisoquinolones" - Poster presentation at RSC Heterocyclic and Synthesis Group, 23rd Postgraduate Heterocyclic Symposium.

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LIST OF ABBREVIATIONS

Å	Angstroms
aq	aqueous
Ar	Aryl
Boc	*tert*-Butoxycarbonyl
Bn	Benzyl
Bz	Benzoyl
Bu	Butyl
conc.	Concentrated
DISC	Death inducing signalling complex
DMF	Dimethylformamide
DPPA	Diphenylphosphoryl azide
d.r.	diastereomeric ration
DR4	Death receptor 4
DTBMP	2,6-Di-*tert*-butyl-4-methylpyridine
ED_{50}	Effective dose
e.e.	Enantiomeric excess
eq.	Equivalents
ESI	Electrospray ionisation
Et	Ethyl
Et_2O	Diethyl ether
EtOAc	Ethyl Acetate
EtOH	Ethanol
EVK	Ethyl vinyl ketone
F-actin	Fibrillary actin
g	Grams
G-actin	Globular actin
GI_{50}	Growth inhibition value
HCl	Hydrochloric acid
hrs	Hours
HPESW	Hajos-Parrish-Eder-Sauer-Wiechert reaction
HPLC	High performance liquid chromatography

HRMS	High resolution mass spectroscopy
Hz	Hertz
IC_{50}	Inhibition constant
IR	Infrared
J	Coupling constant
LDA	Lithium diisopropylamide
M	Moles per litre
m-	*meta*-
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
mg	Milligrams
mins	Minutes
MK2	Mitogen-activated protein kinase-activated protein kinase 2
mL	millilitres
mmol	millimoles
mol	Moles
Mp	Melting point
MS	Mass spectroscopy
MVK	Methyl vinyl ketone
m/z	Mass to charge ratio
NaOH	Sodium hydroxide
NCI	National Cancer Institute
nM	Nanomoles
NMR	Nuclear Magnetic Resonance Spectroscopy
Ns	4-Nitrophenylsulfonyl
o-	*ortho*-
OAc	Acetate
p-	*para*-
Pd/C	Palladium on activated carbon
PE	40-60 °C petroleum ether
Ph	Phenyl
pK_a	Acidity constant

ppm	Parts per million
Pr	Propyl
p-TsOH	*para*-toluenesulfonic acid
R_f	Retention factor
r.t.	Room temperature
SAR	Structure-activity relationship
S_N1	Unimolecular nucleophilic substitution
S_N2	Bimolecular nucleophilic substitution
TBDMS	*tert*-butyldimethylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
tert-	tertiary
t_R	Retention time
tRNA	Transfer ribonucleic acid
UV	Ultraviolet
µg	Micrograms
µL	Microlitres

1. INTRODUCTION

1.1. NARCICLASINE; SYNTHESIS AND BIOLOGICAL ACTIVITY

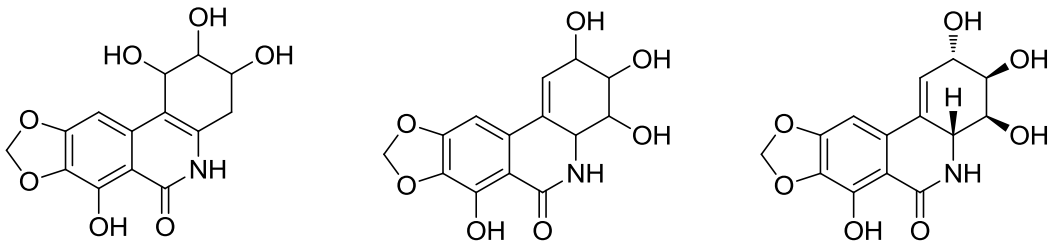
1.1.1. Isolation

The Amaryllidaceae family of plants have long been known to have medicinal properties and there are reports of their use throughout history in treating a number of ailments including cancer. A review by Hartwell found that many of the plants in the family have been used in civilisations across the world and throughout history to treat symptoms of what we now know as cancer.[1] In particular, oil isolated from the bulbs of the plants from the *Narcissus* genus has been used as a treatment by Hippocrates in Ancient Greece and Pliny the Elder in Ancient Rome. Commonly, the plants of the *Narcissus* genus are known as the daffodil. In herbal medicine, Culpeper describes daffodils being used to treat a range of ailments from healing wounds to treating fevers.[2] Daffodils have also been found to have a negative effect on the length of vase life of cut flowers.[3]

Figure 1: Daffodils at University of Bath

Narciclasine has since been discovered to be the compound responsible for these effects. Ceriotti initially described narciclasine as “A potent antimitotic

substance which was isolated from several varieties of *Narcissus* bulbs" in 1967.[4] In the following year, the group published **1** as what they believed to be the structure of narciclasine (Figure 2).[5] Meanwhile, Okamoto *et al.* had isolated lycoricidinol from the bulbs of *Lycoris radiate* and published its structure as **2** along with initial growth inhibition studies.[6] After a chemical study[7] and X-ray crystallography,[8] narciclasine and lycoricidinol were identified as the same substance and the structure was assigned with absolute stereochemistry as **3**.



1 **2** **3**

Figure 2: Debated structures of narciclasine

To date, narciclasine has been isolated from many different plants of the Amaryllidaceae family, but it is found in the bulbs of all species of *Narcissus* genus at 30-200 mg/kg depending on the variety of plant.[9] This yield from the natural sources is not sufficient to progress narciclasine as a clinical candidate. However, there have been many investigations into the biological activity and chemical synthesis of narciclasine and its analogues.

1.1.2. Biological Activity

Narciclasine's anticancer properties were first described in 1967 by Ceriotti when he tested the substance *in vivo* in mice on sarcoma 180 cells, observing an anti-mitotic activity at high doses.[4] Okamoto *et al.* also studied narciclasine and its anti-cancer effects in Ehrlich carcinoma and observed a significant drop in cell viability after treatment with 100 µg of narciclasine over 30 days.[6] Mondon and Krohn published the first structure-activity relationship study in 1975.[10] They found that in HeLa (cervical cancer) and HEP_H (laryngeal cancer) cell lines that narciclasine was toxic in concentrations of >0.1 µg/mL and showed an effect between 0.025-0.1

μg/mL. Since then, narciclasine has been shown to have a number of mechanisms of action for its anti-cancer activity.

In 1975, Vazquez *et al.* published a series of letters investigating the ribosomal mechanism of action of narciclasine in yeast. They found narciclasine blocks peptide synthesis by interacting with the 60S ribosome subunit, preventing the tRNA at the A site of the ribosome binding to the peptidyl-transferase centre so the next amino acid in the sequence cannot be attached to the growing peptide chain (Figure 3).[11] This was proved by studying strains of yeast ribosomes with a mutation in the peptidyl-transferase centre and these strains showed resistance to narciclasine.[12]

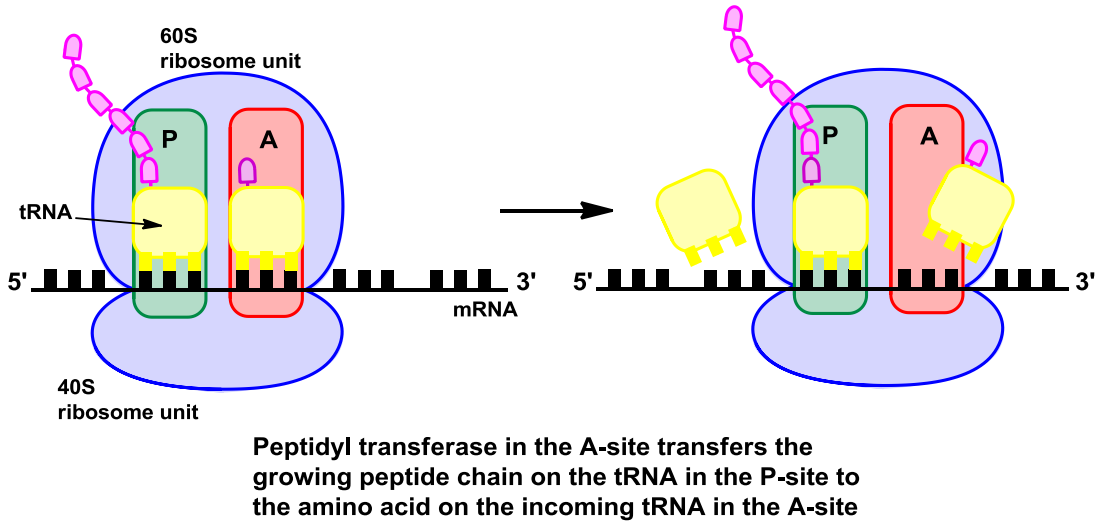


Figure 3: Role of the ribosome in protein synthesis

Kiss *et al.* have shown that narciclasine can induce apoptosis selectively in cancer cells, but not in normal cells.[13] They found that the mechanism for apoptosis is dependent on the type of cancer cell, but in both types of cell apoptosis goes via the death receptor pathway (Figure 4). The cascade begins with the narciclasine-promoted activation of death receptors FAS and DR4, followed by formation of the Death Inducing Signalling Complex (DISC). Procaspase-8 is recruited to DISC and activated to give caspase-8 and it is from here that the two types of cell differ. In type I cells, such as the PC-3 prostate cancer cells, a high concentration of caspase-8 is recruited and activated which in turn directly recruits the effector caspases to

trigger apoptosis.[14] In type II cells, such as MCF-7 breast cancer cells, the recruitment of caspase-8 is low, so further amplification of this signal is required to initiate the effector caspases. This amplification occurs through the mitochondria, affecting the potential of the outer mitochondrial membrane,[15] thus allowing the release of cytochrome c, which forms part of the apoptosome. This structure then activates the effector caspases, triggering apoptosis.[16]

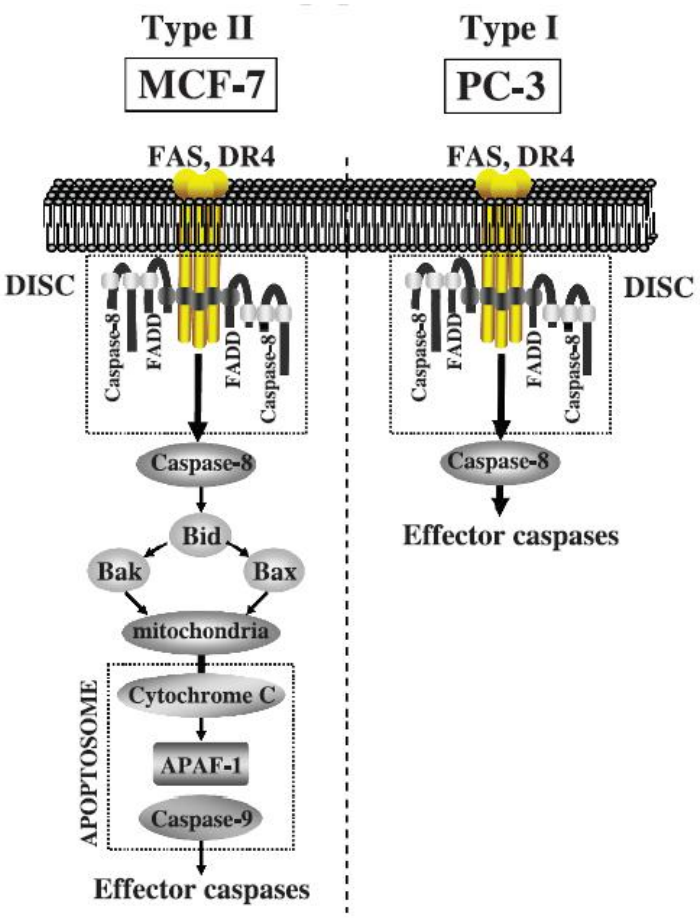


Figure 4: Apoptosis pathways in MCF-7 and PC-3 cells, representing type II and type I cells[13]

These observations nicely complement observations made on pancratistatin, a closely related analogue of narciclasine, which has also found to selectively induce apoptosis in cancer cells[17,18] and leukaemia.[19] There are also no signs of DNA damage caused by pancratistatin in either cancer cells or normal cells. Matching Kiss' observations on effects of narciclasine on MCF-7 breast carcinoma, pancratistatin has shown to affect the mitochondrial membrane potential in SHSY-

5Y neuroblastoma cells, making the outer membrane more permeable and so allowing the release of cytochrome c.[17] However this may be a downstream effect of activation of caspase-3,[18] a protein which is also related to the activation of caspase-8.[20]

Ingrassia and Lefranc have also performed an in-depth study of narciclasine and various analogues.[21] They found that narciclasine impairs cell proliferation and cell migration in cancer cell lines to a greater extent than in normal cell lines (Figure 5). The natural product displays activity in cell lines that are both resistant (e.g. U373 glioblastoma cells) and sensitive (e.g. PC-3 prostate cancer cells) to apoptosis as it works through non-apoptotic mechanisms. These include promoting actin polymerisation, which in turn rigidifies the actin cytoskeleton, impairing growth and movement of the cancer cells (Figure 6).

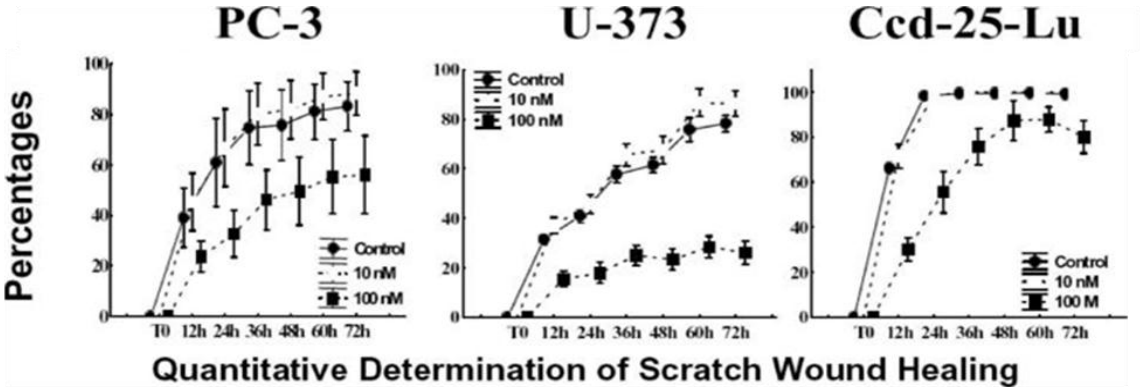


Figure 5: Results from scratch wound healing assays of human PC-3, U373 and Ccd-25-Lu normal human lung fibroblasts

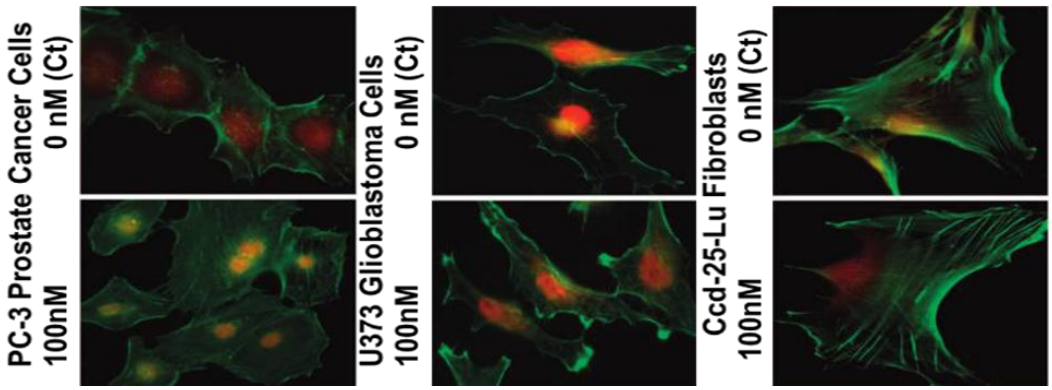


Figure 6: Effects of narciclasine on actin polymerisation in PC-3, U373 and Ccd-25-Lu cells (F-actin shown in green and G-actin shown in red)[21]

This work in the U373 glioblastoma cells has been extended to glioblastomas GL19 and Hs683 and into xenograft models.[22] The investigation found that narciclasine decreases the rate of mitosis by increasing the time between cell division. It decreases cell migration and an increase in fibrillary actin is observed. This effect is due to the activation of Rho, a family of proteins which are key regulators of the actin cytoskeleton (Figure 7). This has the effect of activating its downstream substrates ROCK-1 and LIMK-1 by phosphorylation. Activated LIMK-1 then phosphorylates the Serine3 on cofilin, rendering it inactive. Cofilin is an actin-severing protein, so its inactivation means that the growing actin filaments are not depolymerised, leading to extensive filament formation and cell rigidity, rendering the cell immobile.[23] Although to date, only glioblastoma cells have been investigated for this effect, narciclasine could prove to be effective in other metastasising cell lines, such as breast cancers.

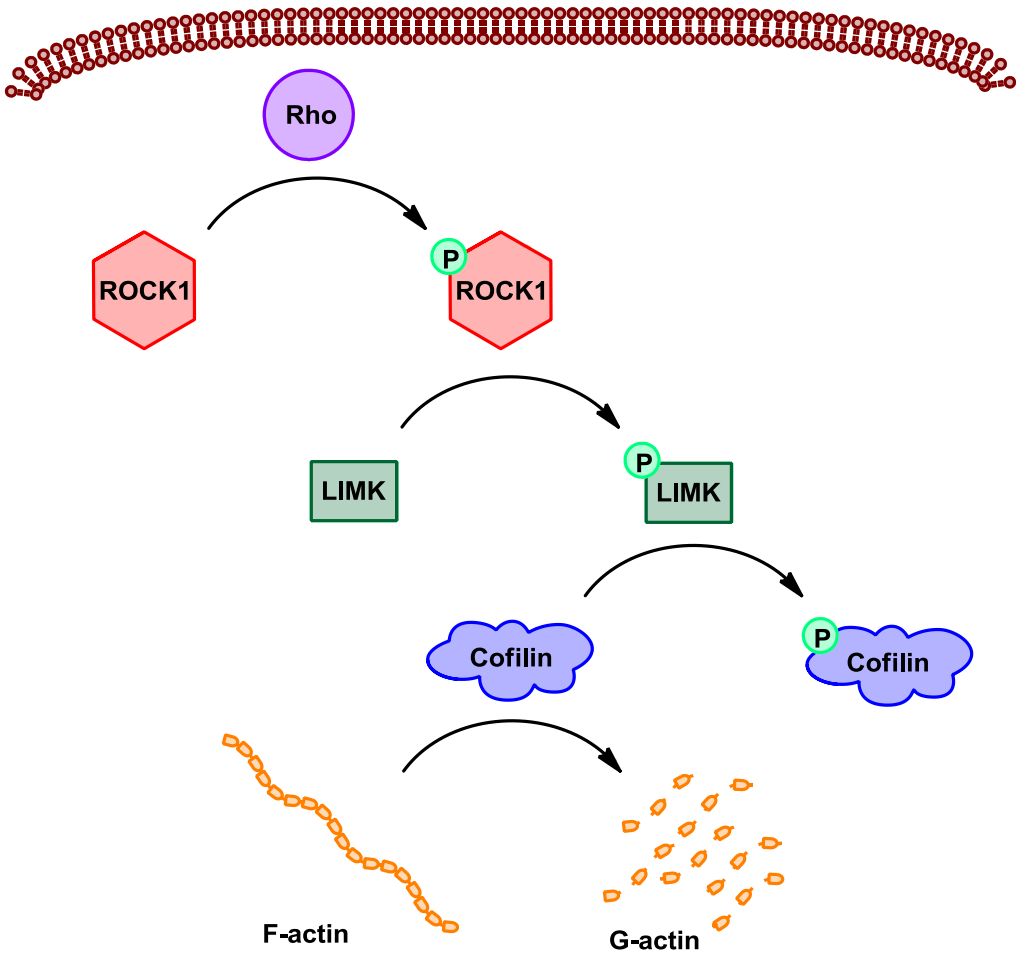


Figure 7: Mechanism of Rho activation leading to increase fibrillary acting within the cell

Despite the many modes of action of narciclasine and its congener pancratistatin, the compounds display a selective anti-cancer activity, whilst showing little effect on normal human cell lines. This gives a strong advantage over many other chemotherapies which have toxicity issues associated with them.

1.1.3. Structure-Activity Relationship

During the numerous investigations on narciclasine, a large number of analogues have been accessed by either isolation from natural sources or synthesised as part of SAR studies or total synthesis attempts. Many of these compounds have been tested for their anti-cancer activity allowing the formation of a structure activity relationship. Narciclasine can be described as a phenanthridinone with a tricyclic core structure consisting of an aromatic, polyoxygenated A-ring, a lactam B-ring and a polyhydroxylated C-ring (Figure 8).

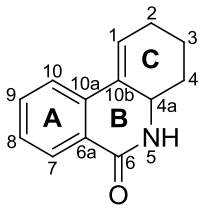
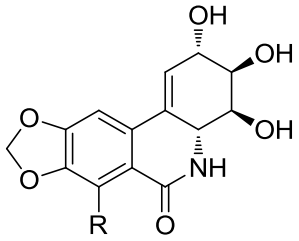
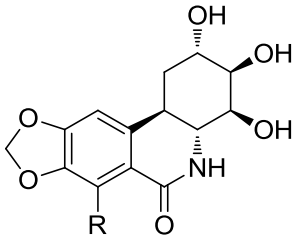


Figure 8: Nomenclature and numbering for the structure of narciclasine

The A-ring in narciclasine **3** has a 7-hydroxy-8,9-methylenedioxy substitution pattern (Figure 9). 7-Deoxynarciclasine **4**, also a natural product shows a 10-fold decrease in mean GI_{50} of 145 nM compared to narciclasine's 15.5 nM in the NCI 60 cell line screen. A decrease in activity is also seen when comparing 7-hydroxy-*trans*-dihydronarciclasine **5** and 7-deoxy-*trans*-dihydronarciclasine **6** with GI_{50} values of 12.6 nM and 67.6 nM, although the difference is not so pronounced.[24]



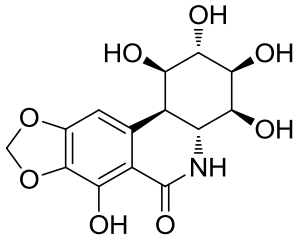
3: R = OH, 15.5 nM
4: R = H, 145 nM



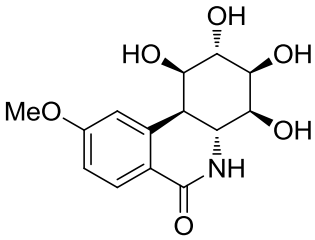
5: R = OH, 12.6 nM
6: R = H, 67.6 nM

Figure 9: Narciclasine 3, 7-deoxynarciclasine 4 and their dihydro-analogues 5 and 6

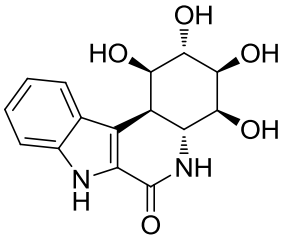
Hudlicky *et al.* have synthesised a number of analogues of the related compound pancratistatin **7** with changes made to the A-ring (Figure 10). The 9-methoxy analogue **8** had an average GI_{50} value of 3.7 µg/mL across 6 solid tumour cell lines and a leukaemia cell line,[25] a 100-fold reduction in activity when compared to pancratistatin's activity of 0.034 µg/mL in the same cell lines. This means that in general there is a 10-fold loss in activity with the removal of each subsequent oxygen group. Hudlicky also synthesised analogue **9** where the A-ring was replaced with an indole, with the reasoning that the NH would mimic the hydroxyl and the aromatic ring would mimic the lipophilic methylenedioxy substituent.[26] The compound was approximately 100-fold less active than pancratistatin in P388 leukaemia and inactive against the 3 human cancer cell lines that were tested showing that despite the modelling comparing the two compounds, they do behave differently in a cellular environment.



7
34 nM



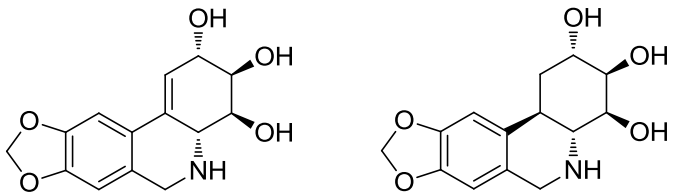
8
3700 nM



9

Figure 10: Pancratistatin 7 and some synthetic analogues

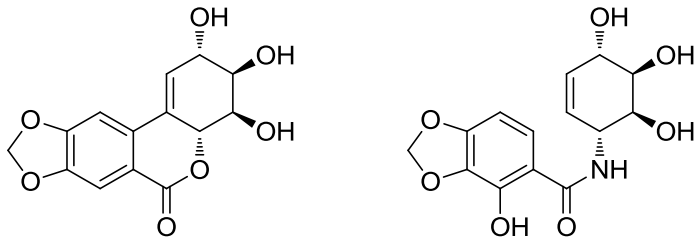
The B-ring in both narciclasine and pancratistatin is a δ-lactam. Reduction of this lactam to a cyclic amine has a detrimental effect on activity. Pettit *et al.* synthesised amines **10** and **11** by reduction of the corresponding amides.[27] The amines and their HCl salts were evaluated against a panel of human cancer cell lines and displayed growth inhibition values of >1 μg/mL compared with those of corresponding amides of <0.15 μg/mL.



10 **11**

Figure 11: Cyclic amine analogues of lycoricidine and dihydrolycoricidine[27]

Chapleur *et al.* have investigated changes to the B-ring, synthesising lactone analogues of narciclasine **12** which were found to be inactive (Figure 12).[28] They also synthesised a series of *seco*-analogues **13** where the A and C-rings were not connected between the 10a and 10b positions and again these were found to be devoid of activity.[29]



12 **13**

Figure 12: Chapleur's B-ring analogues[28,29]

Arylcyclitol analogues have also been reported by Kornienko *et al.* where the B-ring has been removed completely (Figure 13).[30] These have also shown to be completely inactive, complementing Chapleur's findings that the B-ring needs to remain intact with an amide NH for biological activity.

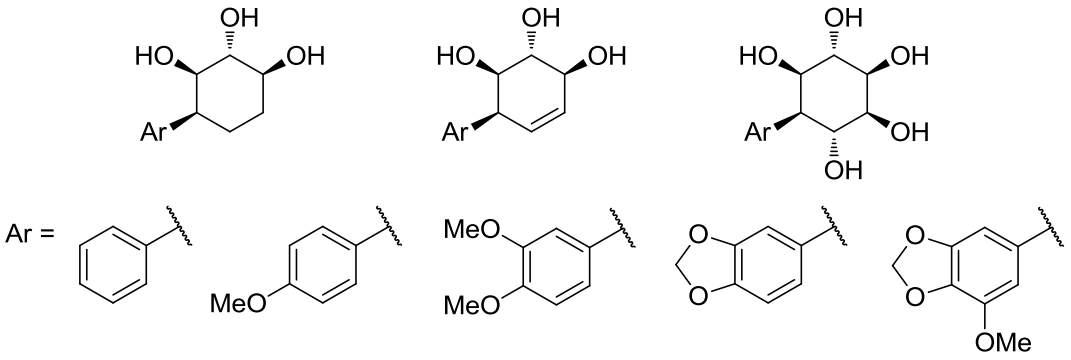


Figure 13: Kornienko's arylcyclitol analogues[30]

Narciclasine **3** has an sp^2 centre at the 10b position and a stereogenic centre at the 4a position which is in the *R*-configuration. Analogues of narciclasine with changes to the ring junction have been isolated from natural sources and tested in the NCI 60 cell line screen (Figure 14).[24] When the ring junction was a double bond between the 4a and 10b positions in **14**, the activity was reduced significantly to 1180 nM. Changing the 10b position to an *R*-configured sp^3 centre to give **5** with a *trans*-geometry at the ring junction had little effect on the activity with a slight increase from 15.5 nM to 12.6 nM. However, when the 10b position was an *S*-configured sp^3 centre, giving **15** with a *cis*-geometry at the ring junction there was a large loss in activity to 380 nM.

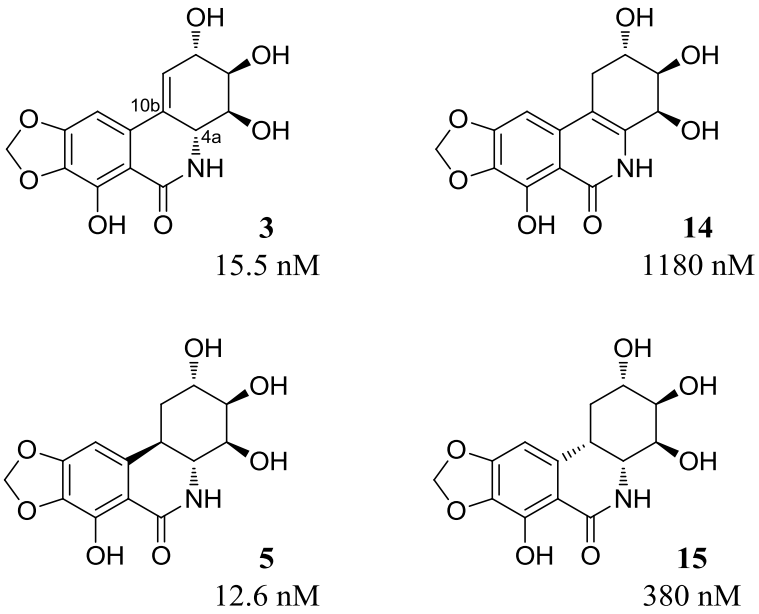


Figure 14: Changes at the B/C-ring junction and its effect on activity[24]

The C-ring in narciclasine can be described as an amino-inositol ring. Many analogues of narciclasine have been isolated or synthesised with changes made in the C-ring. A number of analogues have been made in the *trans*-dihydrolycoricidine series, testing how many hydroxyl groups are needed for activity (Figure 15).[25,31] The mono-alcohol **16** displayed only a moderate activity against P388 murine leukaemia of 40.1 μg/mL, whereas the diols proved to be more active in the same cell line. The 3,4-diol **17** had an ED_{50} of 1.39 μg/mL, but the most active analogue was the 2,3-diol **18** with an ED_{50} of 0.45 μg/mL. This is much less active than pancratistatin (ED_{50} = 0.039 μg/mL) or narciclasine (ED_{50} = 0.0012 μg/mL) in the same cell line; however, a direct comparison should not be drawn as the analogues do not contain the 7-hydroxyl group. The 2,4-diol **19** was not tested against P388 leukaemia, but has been shown to be inactive against MCF-7 breast cancer cells.[32]

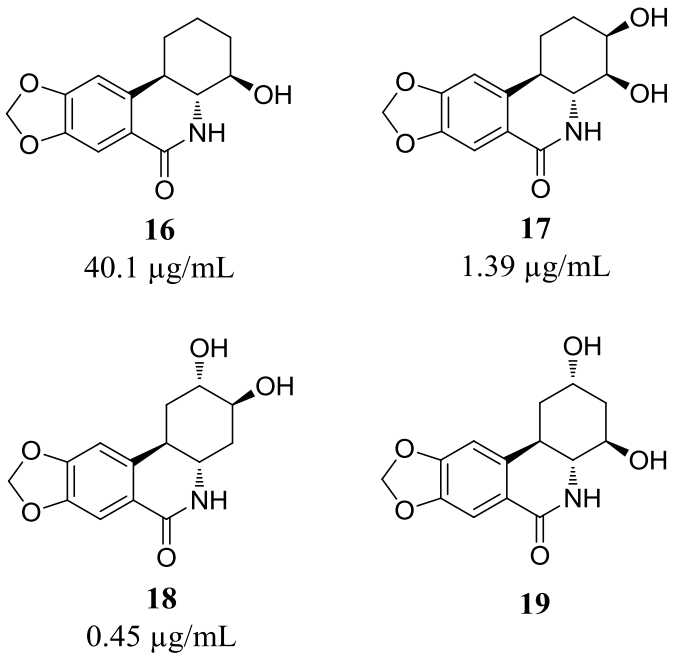
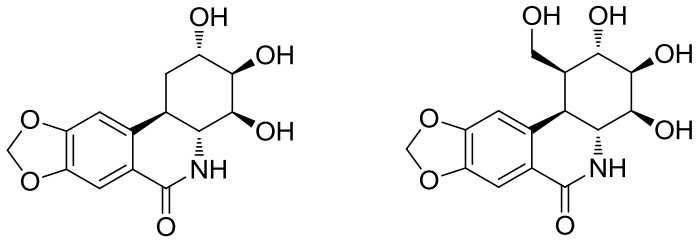


Figure 15: C-ring analogues in the dihydrolycoricidine series

Hudlicky *et al.* have synthesised the C1 homologue of 7-deoxypancratistatin **20**, which showed between 2 and 20 fold loss of activity depending on the cell line when compared to *trans*-dihydrolycoricidine **6** which bears no substituent at the C1 position (Figure 16).[33]

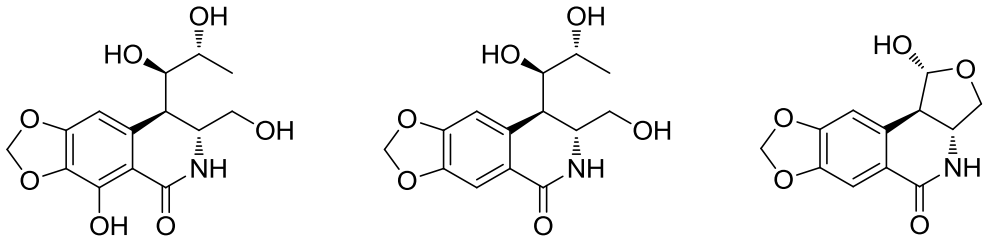


trans-dihydrolycoricidine

6 **20**

Figure 16: C1-homologue of 7-deoxypancratistatin[33]

Kornienko *et al.* have also investigated modifications on the C-ring by opening the ring and contracting the ring to a furan (Figure 17).[34] All three compounds **21**, **22** and **23** showed at 10-12 fold loss in activity in HeLa and MCF-7 cells when compared to narciclasine. The cyclic system is more rigid in the natural product, holding the hydroxyls group in a favourable conformation compared to the acyclic analogues.

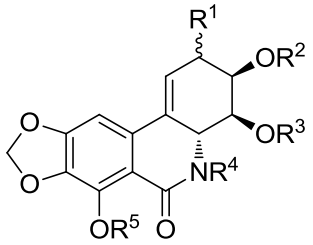


21 **22** **23**

Figure 17: Kornienko's truncated C-ring analogues[34]

A series of 28 analogues based on **24** were synthesized and tested by Ingrassia and Lefranc (Figure 18).[21] They found that protection of all the heteroatoms resulted in a reduction in activity; and in particular, the loss of the NH upon protection of the amide always resulted in a complete loss of activity. The hydroxyl at the C2 position was not sensitive to protection and a range of substituents were attached here without any affect on the activity. The 7-hydroxyl group proved to be much more sensitive, especially towards alkyl substituents, although acyl and sugar substituents were tolerated more. Acetal protection of the 3,4-diol was also tolerated. The only changes in the C-ring that gave comparable

activities to narciclasine were the C2-hydroxyl esters, but this was not surprising as it was found on closer inspection that these decomposed in the biological media to give narciclasine.



24

R^1 = OH, OAc, OBz, OTBDMS, propanoate, isobutyrate
R^2 = H, OAc,
R^3 = H, OAc
R^4 = H, CH_2CO_2Et, Et, Bn
R^5 = H, CH_2CO_2Et, Ac, Bz, Et, glucose

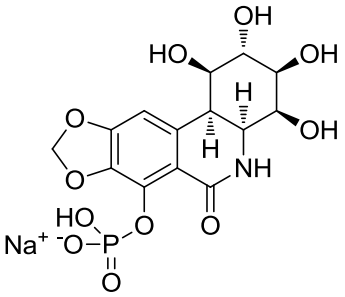
Figure 18: General structure and substituents of synthesised analogues of narciclasine[21]

In summary for biological activity, the A-ring needs to be a poly-oxygenated aryl ring, the B-ring must be a lactam, with the 4a position in the *R*-configuration and the 10b position either being sp^2 or in the *R*-configuration. The C-ring should be cyclised and contain a minimum of three hydroxyl groups.

1.1.4. Pro-drug Synthesis

A major problem with advancing narciclasine or its analogues as clinical candidates has been the poor solubility of the compounds; pancratistatin has a solubility of only 53 µg/mL. To overcome this, pro-drugs have been investigated. Work has mostly been performed on pancratistatin **7** rather than narciclasine **3**, but the ideas can be applied to both compounds. Pancratistatin has 5 free hydroxyl groups and these provide the perfect handles to make pro-drugs. Synthesis of phosphate esters has been the most investigated method of making pancratistatin and narciclasine more soluble.

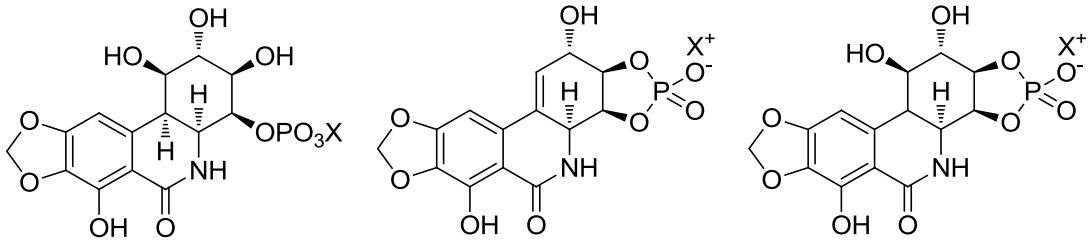
The sodium 7-O-phosphate **25** has a greatly improved aqueous solubility of 20 mg/mL at 25 °C and showed comparable activities against a panel of cancer cell lines when compared to pancratistatin (Figure 19).[35] Other counterions were also investigated and showed a range of solubility and activity values.



25

Figure 19: Sodium pancratistatin-7-O-phosphate 25

A number of 4-O-phosphate esters of pancratistatin **26** and 3,4-O-cyclic phosphate esters of narciclasine **27** and pancratistatin **28** have also been synthesised and tested against a panel of cancer cell lines (Figure 20).[36] Generally, the phosphates showed a 10-fold reduction in activity when compared to the parent compounds but this was dependant on the cell line and the counterion used. The solubility of these compounds has not been assessed quantitatively as the increase in solubility had previously been demonstrated with **25**. The improved solubility of sodium pancratistatin 3,4-O-cyclic phosphate **28** has allowed *in-vivo* studies to be performed in Human colon tumour xenograft models. At 100 mg/kg, **28** gave an increase in tumour necrosis and a disruption in mitochondrial membrane potential was also observed, complementing the *in-vitro* observations.[37]

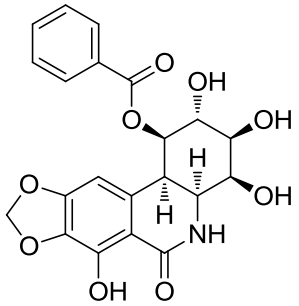


26 **27** **28**

Figure 20: Pancratistatin-4-O-phosphates 26, narciclasine-3,4-O-cyclic phosphates 27 and pancratistatin-3,4-O-cyclic phosphates 28

Phenstatin **29** is the 1-benzoyl adduct of pancratistatin and displays up to a 300-fold increase in activity across a panel of 6 cell lines when compared to pancratistatin and up to an 80-fold increase when compared to narciclasine across the same cell lines (Figure 21).[36,38] However, as the solubility of phenstatin has not been

determined, it is not known whether this increase is due purely to improvements in solubility or due to improved potency.



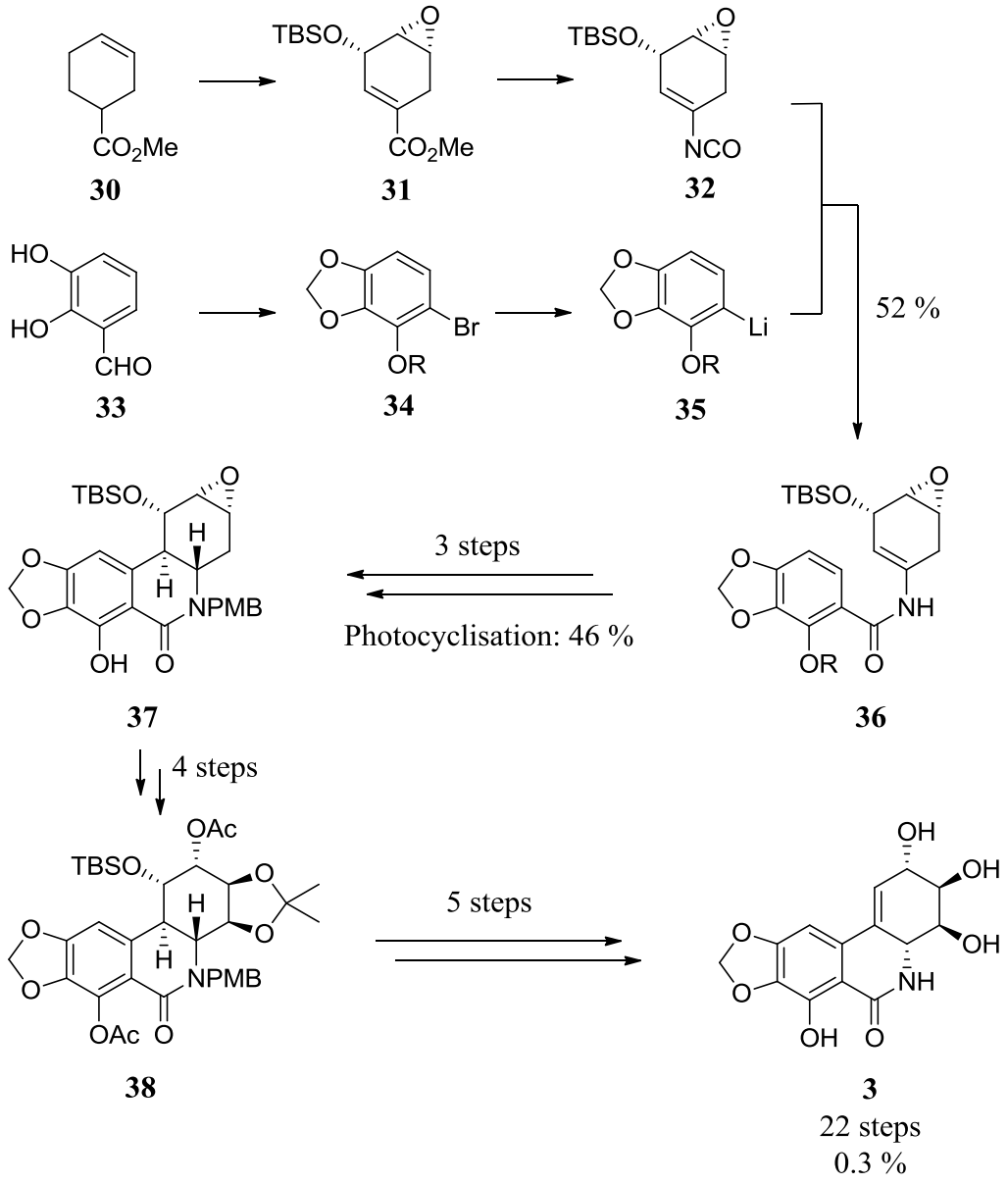
29

Figure 21: Phenstatin 29

1.1.5. Synthetic Attempts

Since 1997 there have been four syntheses of narciclasine, each taking a different approach.

Rigby *et al.* published the first total synthesis of narciclasine **3** in 1997 in 22 steps and 0.3 % overall yield (Scheme 1).[39] In this approach, the A-ring originated from 2,3-dihydroxybenzaldehyde **30** and the C-ring is synthesised from methyl cyclohex-3-ene carboxylate **33**. The two portions were connected by capturing the isocyanate **32** with the aryl lithium carbanion **35** to give the amide **36** in 52 % yield. Then a photochemical cyclisation formed the bond between the 10a and 10b positions in 46 %. The C-ring was manipulated to install the hydroxyl substituents and finally deprotection revealed the natural product **3**.

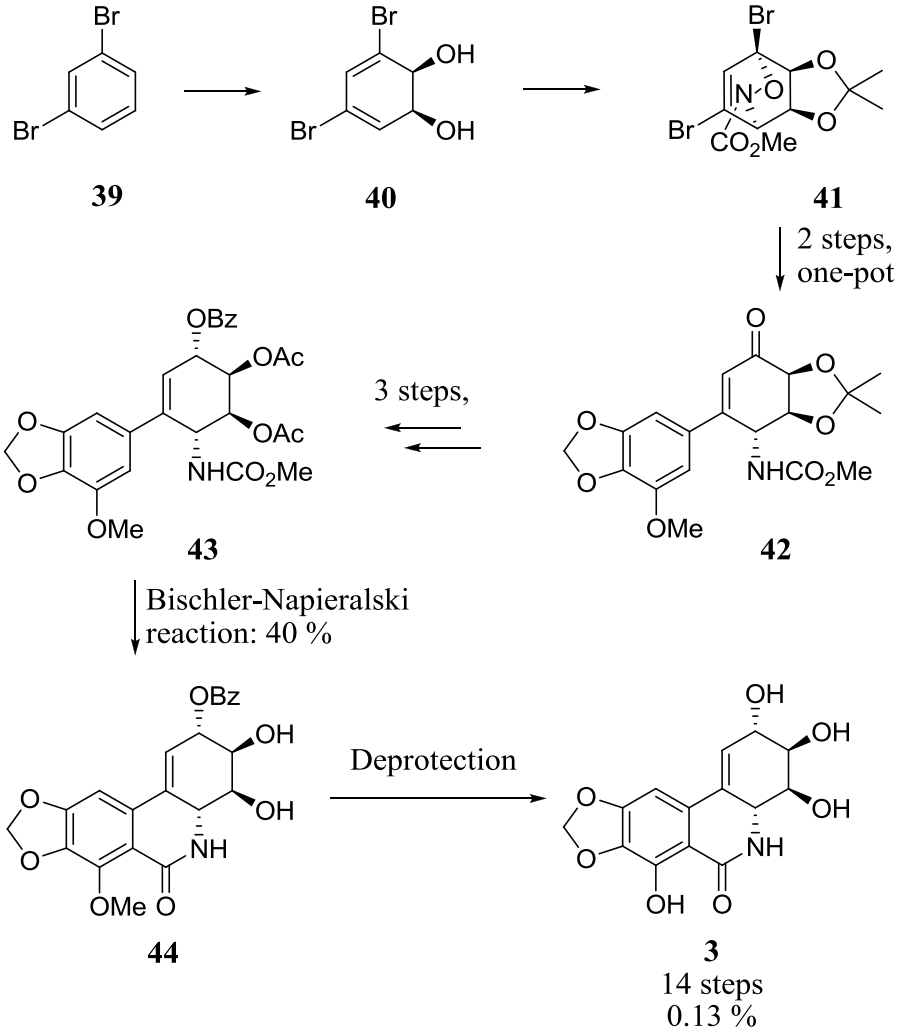


Scheme 1: Rigby's synthesis of narciclasine[39]

Although Rigby reported the first total synthesis, the step count and overall yield was poor. This was addressed in 1999 when two different syntheses were published by Hudlicky and Keck.

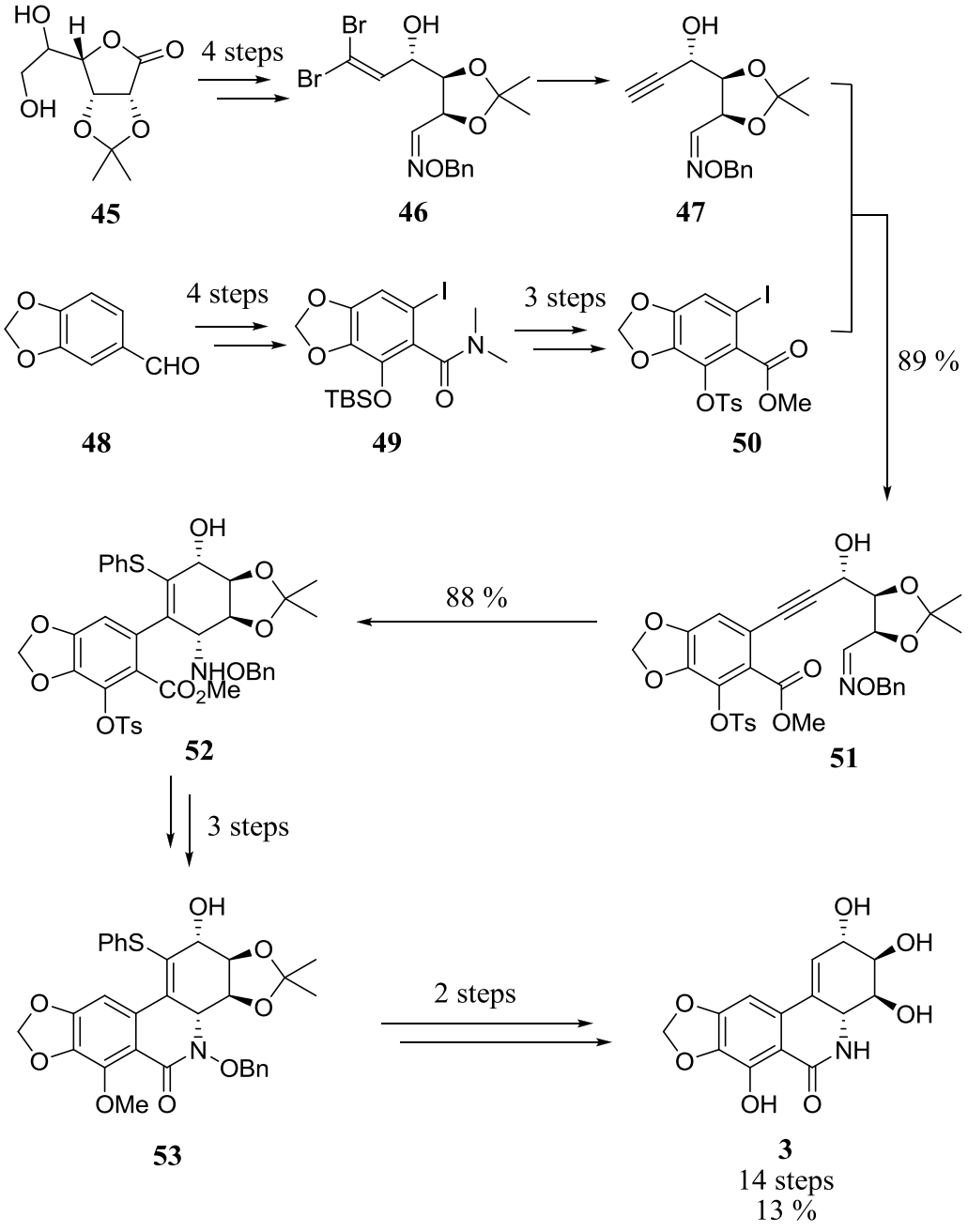
Hudlicky has a great interest in enzymatic dihydroxylation, which was used as a key step together with a Diels-Alder reaction in the synthesis of the C-ring. The A-ring originated from *o*-vanillin and was transformed in four steps into the borate coupling partner for a Suzuki reaction with the C-ring bromide **41**. A modified Bischler-Napieralski reaction formed the B-ring lactam **44** in 40 %. Finally

deprotection revealed narciclasine **3** in a much improved 14 steps from *o*-vanillin but a poorer overall 0.13 % yield (Scheme 2).[40]



Scheme 2: Hudlicky's synthesis of narciclasine[40]

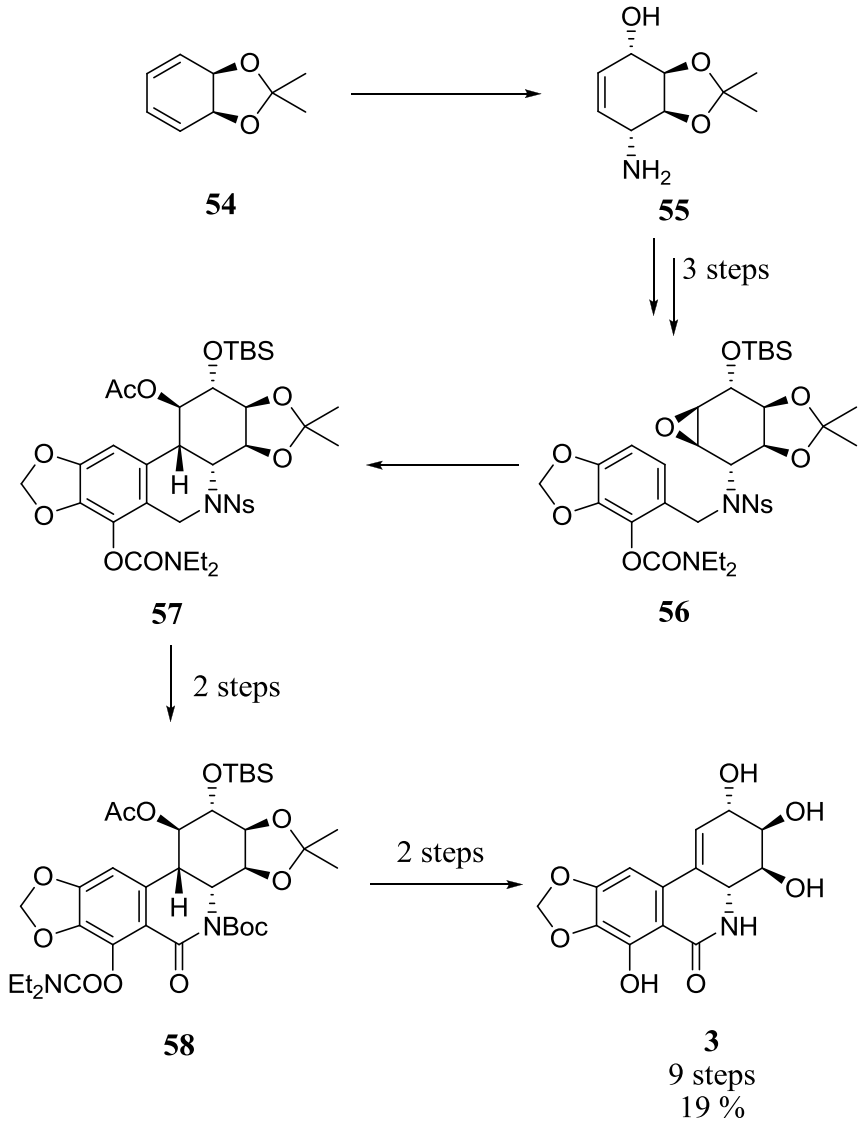
Keck *et al.* used a radical cyclisation as the key step in his synthesis to form the C-ring (Scheme 3).[41] His approach employed a Sonogashira coupling of alkyne **47** and aryl iodide **50** to provide the precursor **51** for the radical cyclisation in 89 % yield. After the radical cyclisation, the AC-ring intermediate **52** was isolated in an excellent 88 %. A number of transformations were then required to cyclise the B-ring, remove the thioether installed during the radical reaction and deprotect the hydroxyl groups to reveal the natural product **3** in 14 steps and a much improved 13 % overall yield.



Scheme 3: Keck's synthesis of narciclasine[41]

Yan *et al.* published the most recent synthesis of narciclasine in 2002, a 9 step route in a 19 % overall yield, making it the most efficient synthesis of the natural product to date (Scheme 4).[42] This synthesis used the same disconnections as Rigby *et al.*, but instead the A-ring is tethered to the C-ring by an *N*-alkylation to afford amine **56,** then the A/C-ring junction was formed by the ring opening of an epoxide to give the tricyclic compound **57**. An oxidation step afforded the amide **58**

and further manipulations gave the natural product **3**. As with Hudlicky's synthesis, the oxygenation pattern in the C-ring is set early on before the cyclisation of the B-ring.



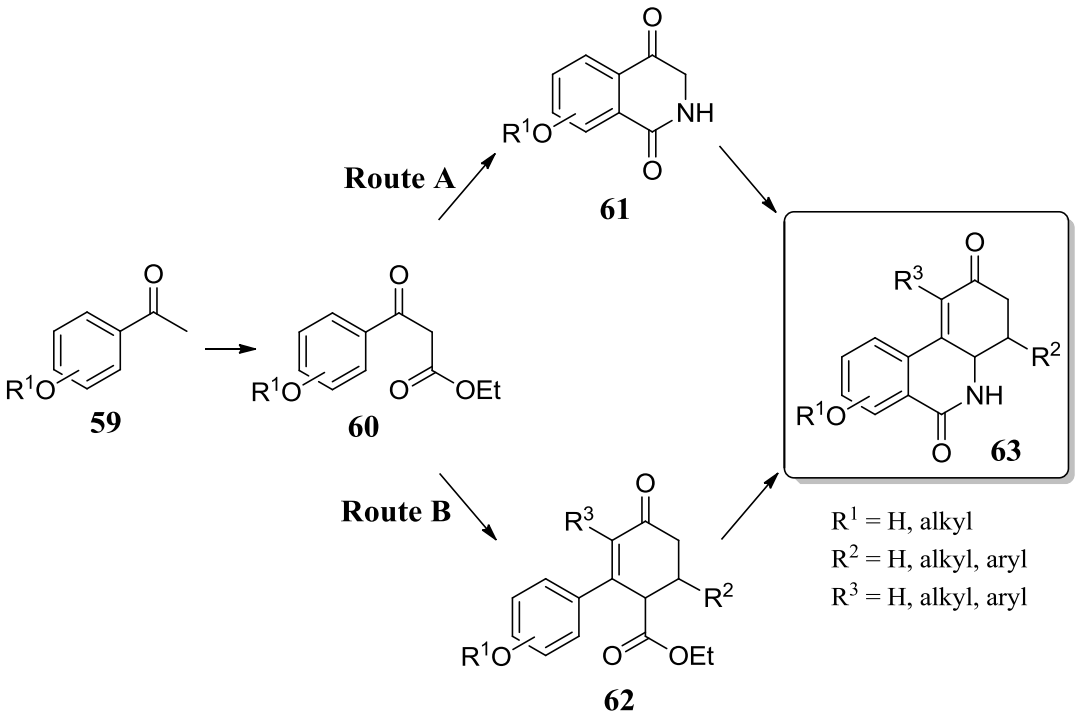
Scheme 4: Yan's synthesis of narciclasine[42]

Despite the improvements to the synthesis of narciclasine, the step counts and yields are still less than desirable for taking the natural product forward as a clinical candidate. These approaches have targeted the natural product for academic interest and to develop new chemical reactions; however, they are not ideal for use in creating libraries of compounds to further investigate structure-activity relationships. To efficiently build libraries of biologically active analogues, an efficient synthesis

of a late-stage intermediate is required, which can then be easily functionalised to give a diverse set of compounds. Developing a route based on this approach should enhance the appeal of the compound as a clinical candidate.

1.2. PROPOSED SYNTHESIS OF ANALOGUES

The initial target of the synthesis will be the tricyclic late stage intermediate **63**. This intermediate can be made from simple commercially available starting materials and there is scope for it to be easily functionalised at several of stages within the synthesis to generate diverse libraries of compounds.

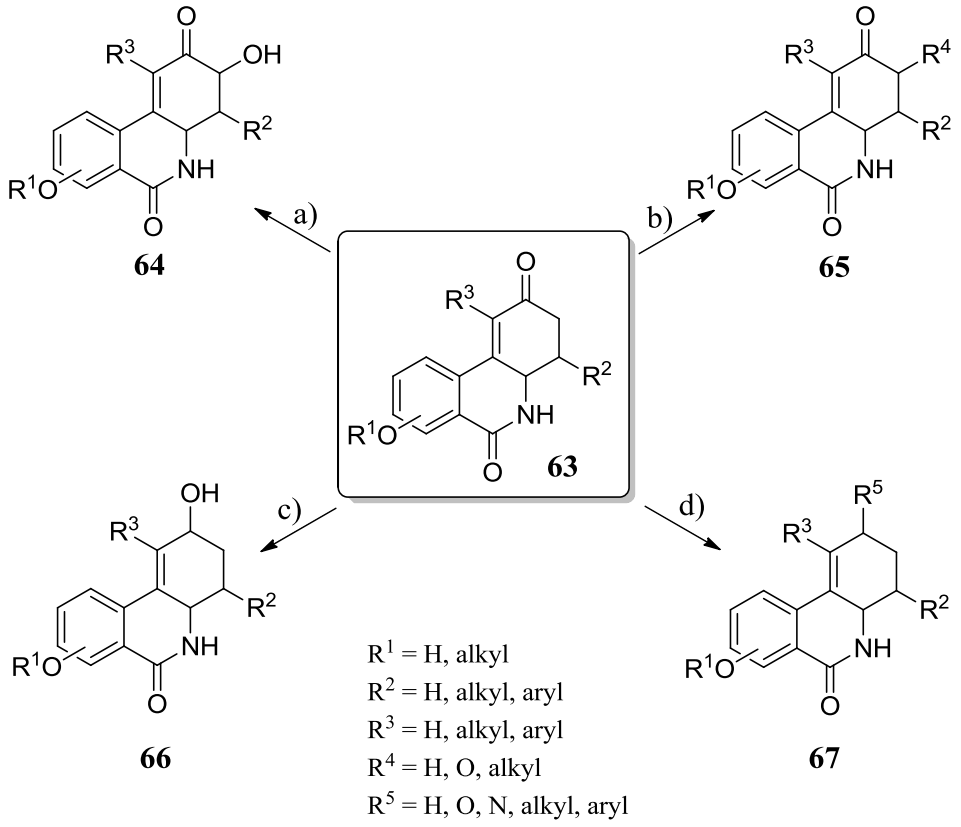


Scheme 5: Proposed synthesis of ABC-ring analogues

The synthesis will begin with the condensation of an acetophenone **59** to generate a β-ketoester **60** (Scheme 5). There are many acetophenones commercially available, allowing different substitution patterns to be investigated on the A-ring. There are two available routes from the β-ketoester to the tricyclic core **63**. In route A, the acid generated from saponification of the β-ketoester will undergo a Curtius rearrangement and intramolecular Friedel-Crafts acylation to give the AB-ring

lactam **61**. This will be followed by a Robinson annulation with a vinyl ketone to install the C-ring. Route B will use the same reactions but applied in the opposite order, so the β-ketoester will be condensed with a vinyl ketone in a Robinson annulation to give a modified Hagemann's ester **62**. After saponification of the ester, the acid will then undergo a Curtius rearrangement and intermolecular Friedel-Craft acylation to give the B-ring lactam **63**. The Robinson annulations will be optimised using methyl vinyl ketone (MVK), however a range of vinyl ketones can be used to install functional groups at the C1 and C4 positions of the phenanthridone core.

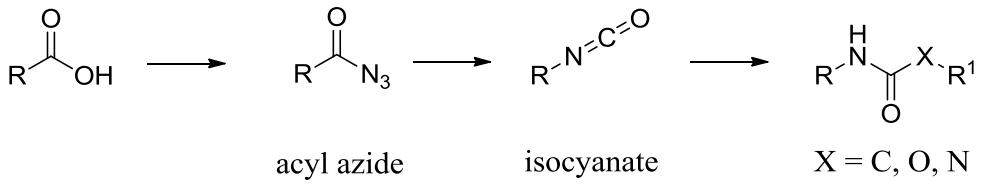
Once the intermediate **63** has been synthesised, a range of methods are available to decorate the C-ring further with different functional groups. For example, the ketone can undergo Rubottom oxidation to install a hydroxyl group at the C3-position (Scheme 6a). Enolate chemistry can be used to install a number of functional groups at the C3 position (Scheme 6b). The ketone can also be reduced to the alcohol using a Luche reduction (Scheme 6c) and the hydroxyl group substituted by different nucleophiles to give variation at the C2 position (Scheme 6d).



Scheme 6: Possible methods to further functionalise the C-ring

1.3. THE CURTIUS REARRANGEMENT

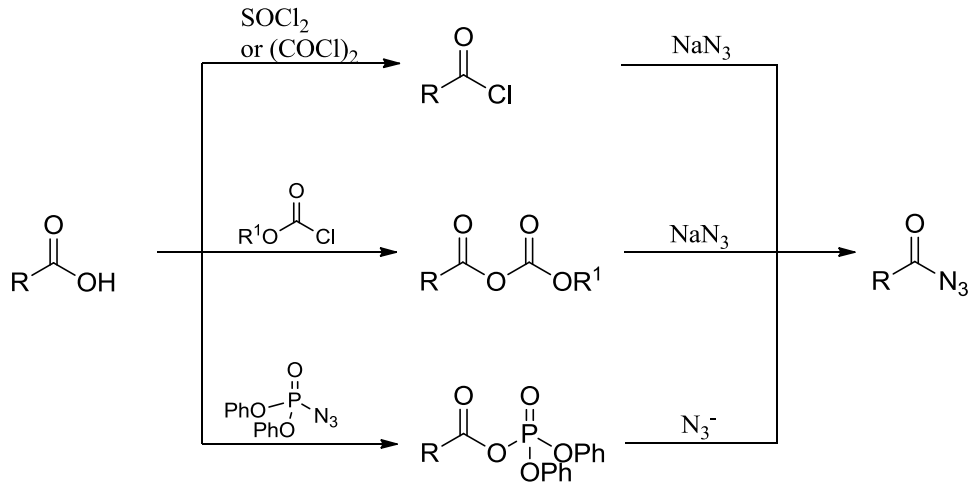
The Curtius rearrangement is the thermal decomposition of an acyl azide, generated from a carboxylic acid, to an isocyanate with the loss of nitrogen. The isocyanate can then be trapped with a range of nucleophiles to afford various groups such as amines, amides, carbamates or ureas (Scheme 7).



Scheme 7: The Curtius rearrangement

Curtius first described the rearrangement of acyl azides in 1890,[43] and in the following years published a number of papers investigating the reaction.[44] There have been a number of reviews into the rearrangement, experimental procedures and its applications,[45,46,47] including the comprehensive review of the first 50 years of the reaction by Smith.[48]

There are several methods of accessing the acyl azide from the carboxylic acid, as there are many ways of activating the carboxylic acid towards nucleophilic substitution including three commonly used methods (Scheme 8). The acid can be converted to the acid chloride using oxalyl chloride,[49] or thionyl chloride.[50,51] Alternatively, the acid can be activated as the mixed anhydride using a chloroformate, as described by Weinstock.[52] This approach has been taken by Ohta and Kimoto in their synthesis of lycoricidine,[53] where they used ethyl chloroformate in the presence of base to form the mixed anhydride. In both of these methods, an external source of azide is added to the reaction to form the acyl azide and an aqueous wash is performed before the reaction is heated to promote the rearrangement. The third method of activating the acid is to use diphenylphosphoryl azide (DPPA) to generate the phosphoryl ester. The use of DPPA for the Curtius rearrangement was first reported in the synthesis of urethanes by Yamada *et al.*[54] They also commented on the ease of the experimental procedure as DPPA acts to both activate the acid and provide a source of azide and that the reaction proceeds without racemisation of existing stereocentres.



Scheme 8: Three commonly used methods of activating the carboxylic acid

The rearrangement of the acyl azide is normally induced thermally; however photolytic,[55] protic acid[56] and Lewis acid [57] catalysed methods have also been reported. The mechanism for the rearrangement could follow two possible mechanisms (Figure 22). In the concerted mechanism, the loss of nitrogen and the migration of the R-group occur at the same time. Alternatively, initial elimination of nitrogen leads to an electron deficient nitrene intermediate which then rearranges to give the isocyanate. There is much debate over the mechanism, but under thermal conditions, it is most likely to proceed via the concerted mechanism, as the nitrene intermediate was not trapped in investigations by Hauser *et al.*[58] and Lowowski *et al.*[59,60]

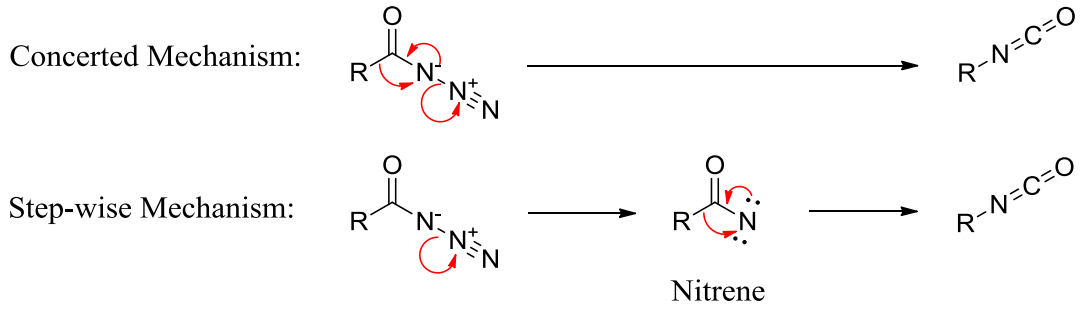
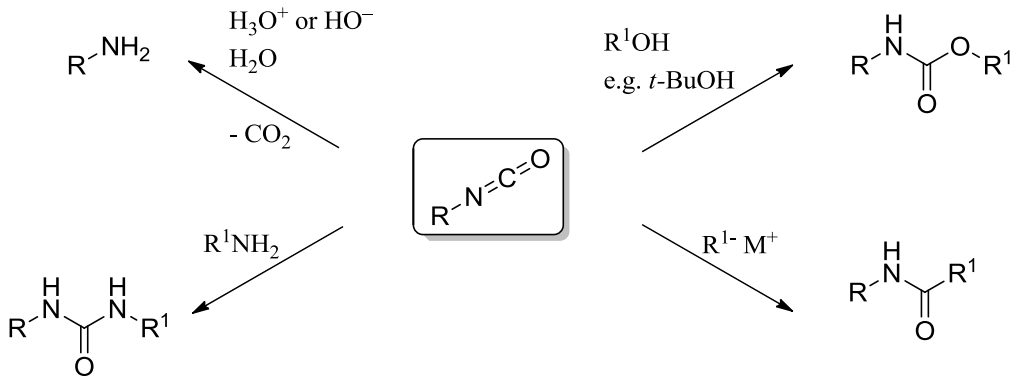


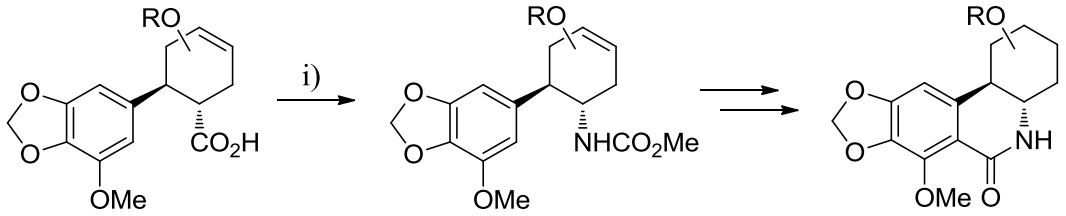
Figure 22: Two mechanisms of isocyanate formation

A number of products can be generated from the isocyanate by adding different nucleophiles to the reaction mixture (Scheme 9).



Scheme 9: Products formed by the addition of different nucleophiles to the isocyanate

The free amine can be accessed by adding aqueous acid or base to the isocyanate, as initially the carbamic acid is formed which decomposes with the loss of carbon dioxide to reveal the amine.[61] The reaction can be performed using an alcohol as the solvent, which traps the isocyanate once it is formed to give a carbamate.[62] In particular, *t*-BuOH can be used as the nucleophile, giving a Boc-protected amine as the product.[63] This is an approach which has been taken in the synthesis of pancratistatin; Kim *et al.* used a Curtius rearrangement to transform a carboxylic acid **68** on the C-ring to a methyl carbamate **69**. The aryl ring was then reacted with the carbamate in a Bischler-Napieralski reaction give the B-ring lactam **70** (Scheme 10).[64]



68 **69** **70**

Reagents and conditions: i) a) DPPA, Et_3N, toluene, reflux, 15 hrs; b) NaOMe, MeOH, reflux, 0.5 hr

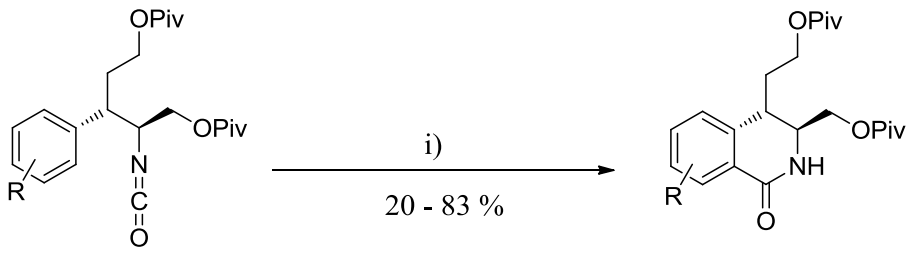
Scheme 10: Kim's use of the Curtius rearrangement in the synthesis of pancratistatin[64]

A number of carbon-based nucleophiles have also been described giving amide products. Padwa *et al.* reported the addition of Grignard reagents to an isocyanate to form a series of 2-amidofurans.[50] In Trost's synthesis of pancratistatin, an isocyanate was trapped by a tethered aryl lithium to give the B-ring lactam,[65] and

in Rigby's synthesis of narciclasine, a vinyl isocyanate was trapped by an aryl lithium in an intermolecular reaction to give the amide bond which would later form part of the B-ring (Scheme 1, p. 16).[39]

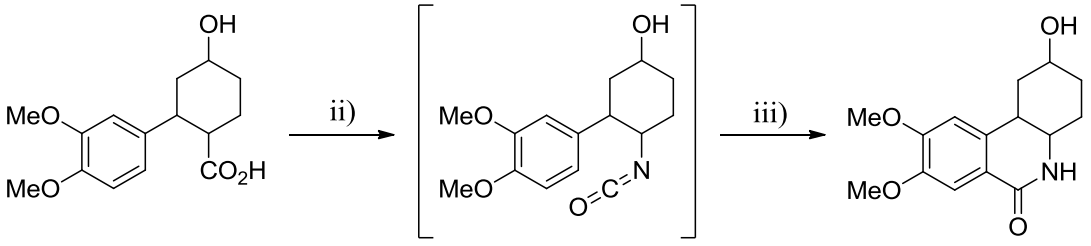
Electron rich aromatic rings have been used as nucleophiles, although the addition is often promoted by Lewis acids. Boron trichloride has been used by Piccolo *et al.* to catalyse the *ortho*-acylation of a phenol with an isocyanate.[66] $AlCl_3$ has also been described to catalyse the addition to an isocyanate (Scheme 11). Hanessian *et al.* used $AlCl_3$ to catalyse the addition of a tethered aromatic ring to an isocyanate **71** to form tetrahydroisoquinolinones **72** in good yields.[67] Afarinkia *et al.* also used $AlCl_3$ in their synthesis of phenanthridones to catalyse the addition of the aryl A-ring to the isocyanate on the C-ring giving the B-ring lactam **75**.[68]

Hanessian *et. al.*[67]



71 **72**

Afarinkia *et. al.*[68]



73 **74** **75**

24% (over two steps)

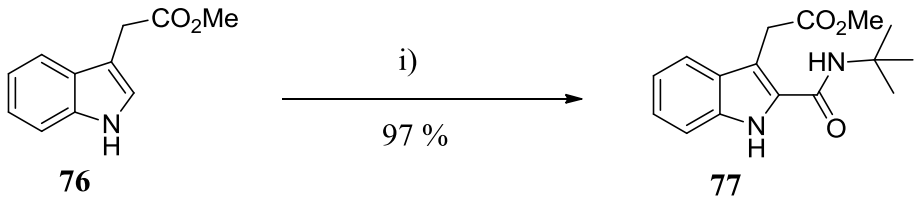
Reagents and conditions: i) $AlCl_3$, CH_2Cl_2, r.t. 12 hrs; ii) DPPA, Et_3N, benzene, 0 °C to r.t., 5 hrs; iii) $AlCl_3$, CH_2Cl_2, r.t., 15 hrs.

Scheme 11: $AlCl_3$-catalysed intramolecular addition of a tethered aryl ring to an isocyanate

$BF_3{\cdot}OEt_2$ is a commonly used Lewis acid and has been employed to the promote addition of an aryl ring to an isocyanate. Hilton *et al.* successfully acylated

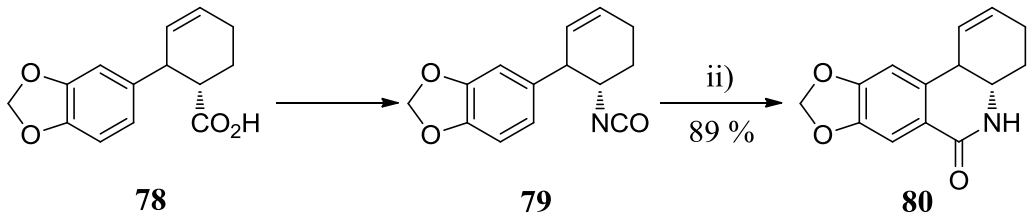
indoles using *tert*-butylisocyanate catalysed by $BF_3{\cdot}OEt_2$ to afford 2-amidoindoles **77** (Scheme 12).[69] Ohta and Kimoto treated the isocyanate **79** with $BF_3{\cdot}OEt_2$ to promote the cyclisation to the lactam **80** in their synthesis of lycoricidine.[53] Finally and possibly most interestingly in the synthesis of narciclasine analogues, Tőke *et al.* used $BF_3{\cdot}OEt_2$ to promote addition to an isocyanate and cyclisation to give the tricyclic core **82**.[70] However, they also noted that when the substrate contained a methoxy- group at the 7-position, $BF_3{\cdot}OEt_2$ also promoted selective demethylation to give the substitution pattern seen in the A-ring of narciclasine.

Hilton *et. al.*[69]



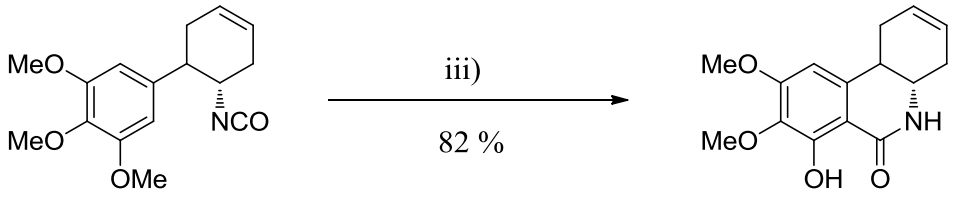
76 **77**

Ohta and Kimoto[53]



78 **79** **80**

Tőke *et. al.*[70]



81 **82**

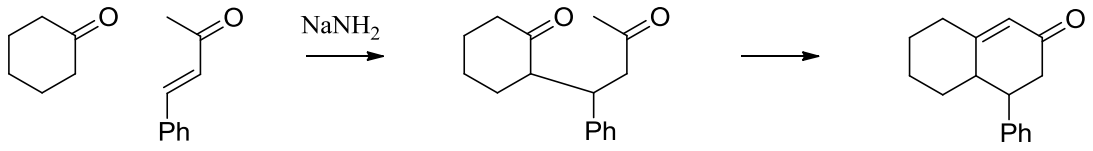
Reagents and conditions: i) *t*-BuNCO, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 ºC; ii) $BF_3{\cdot}OEt_2$; iii) 1:1 $BF_3{\cdot}OEt_2$:Et_2O, 0 ºC, 2 hrs

Scheme 12: Examples of $BF_3{\cdot}OEt_2$ catalysed addition of aryl rings to isocyanates

The examples of Afarinkia *et al.*, Tőke *et al.* and Ohta and Kimoto are of particular interest to this project due to their use in the synthesis of narciclasine analogues. Afarinkia *et al.* accessed the carboxylic acid precursor in only 3 steps, giving only a 4-step synthesis of the tricyclic core structure. Tőke *et al.* generated the isocyanates from the corresponding carboxylic acids; however, they do not report the route they used to make the carboxylic acids. Ohta and Kimoto synthesised the tricyclic core in 4 steps from a benzaldehyde and then manipulated the C-ring the incorporate the hydroxyl groups. These examples prove that the Curtius rearrangement is a viable method of cyclising the B-ring, however they have not been investigated further as a synthetically practical and high yielding reaction in the synthesis of narciclasine analogues.

1.4. THE ROBINSON ANNULATION

The Robinson annulation was discovered by Robert Robinson in 1935 whilst he was working on the synthesis of sterol derivatives.[71] He found that the sodium enolate of cyclohexenone **83** reacted with methyl styryl ketone to give cyclohexenone **85** (Scheme 13).



83 **84** **85**

43 %

Scheme 13: Reaction of cyclohexanone and methyl styryl ketone using sodamide

Reviews by Gawley[72] and Jung[73] discuss the mechanism and applications of the Robinson annulation, showing how the reaction has become a staple of the chemists' toolbox. The reaction has been used in the synthesis of many natural products to build the carbon skeleton, including milbemycin **86**,[74] tanabalin **87**,[75] lycorine **88**,[76] aspidospermidine **89**[77] and codeine **90**[78] (Figure 23).

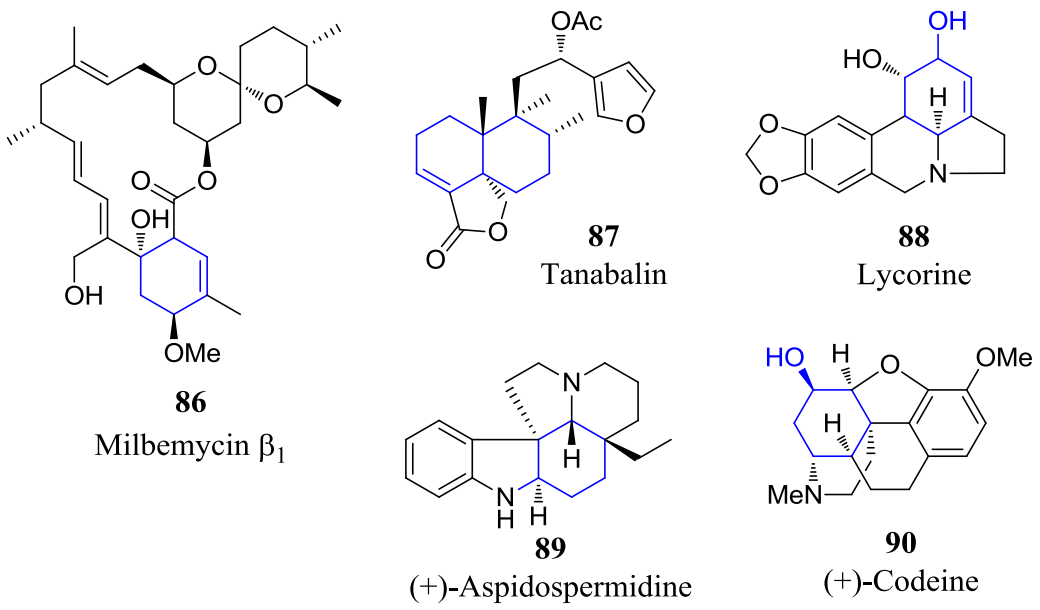
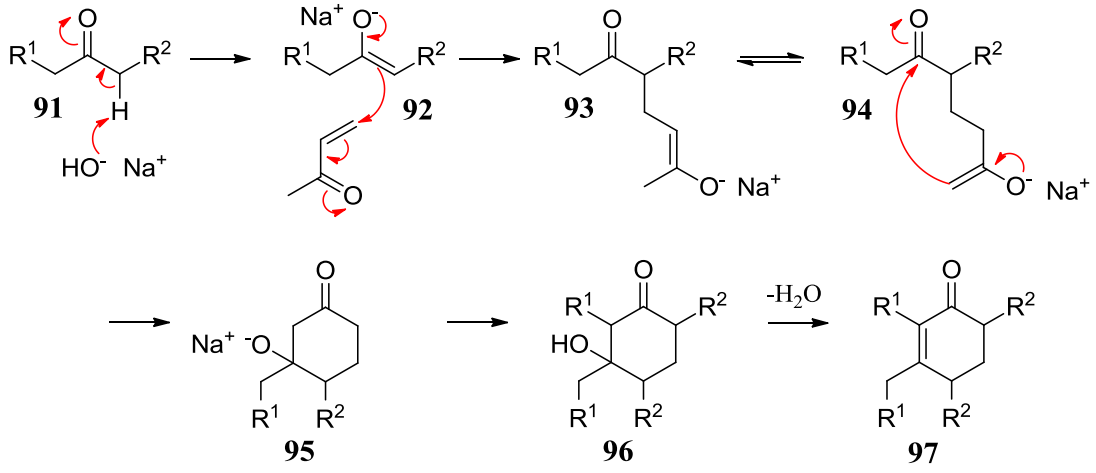


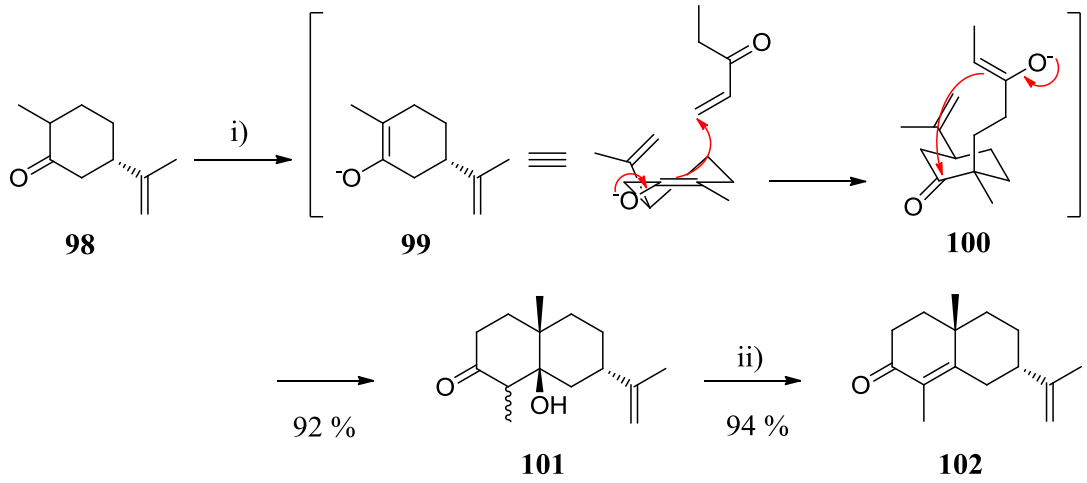
Figure 23: Application of the Robinson annulation in the synthesis of natural products with the rings synthesised using the annulation highlighted.

The Robinson annulation proceeds via a Michael addition followed by an intramolecular aldol cyclisation, as shown by the mechanism in Scheme 48. Typically the reaction is performed by making a sodium enolate **92** using either NaOH or NaOMe/NaOEt and treating it with a Michael acceptor such as methyl vinyl ketone. The product of the conjugate addition is also an enolate **93** which can isomerise to give enolate **94** and then react nucleophilically with the ketone in an intramolecular aldol reaction to form a 6 membered ring **95**. Finally, dehydration installs the double bond to give conjugated cyclohexenone **97**.[72]



Scheme 14: Mechanism of the Robinson annulation[72]

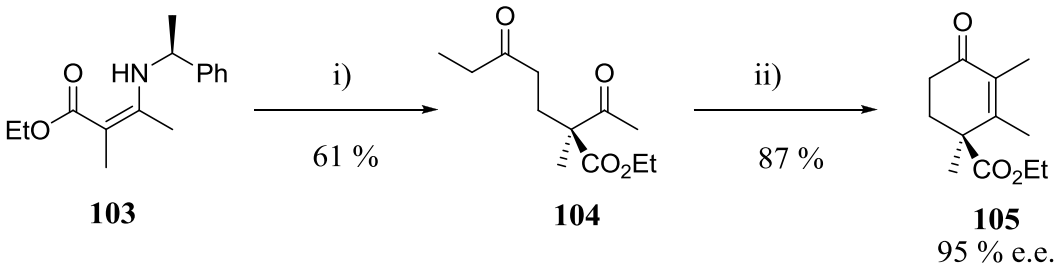
An aprotic variation using the strong base LDA in THF was reported in 1983 to give a regioselective annulation of dihydrocarvone **98** with ethyl vinyl ketone (EVK) to give the bicyclic enone **101** (Scheme 15).[79] The regioselectivity arises from the formation of the thermodynamic enolate **99**, which reacts with the EVK selectively at the axial position to give the intermediate **100** in the thermodynamically favourable chair conformation.



Reagents and conditions: i) LDA, EVK,THF, -78 ºC; ii) KOH, EtOH, heat, 1hr.

Scheme 15: Aprotic variation of the Robinson annulation using LDA

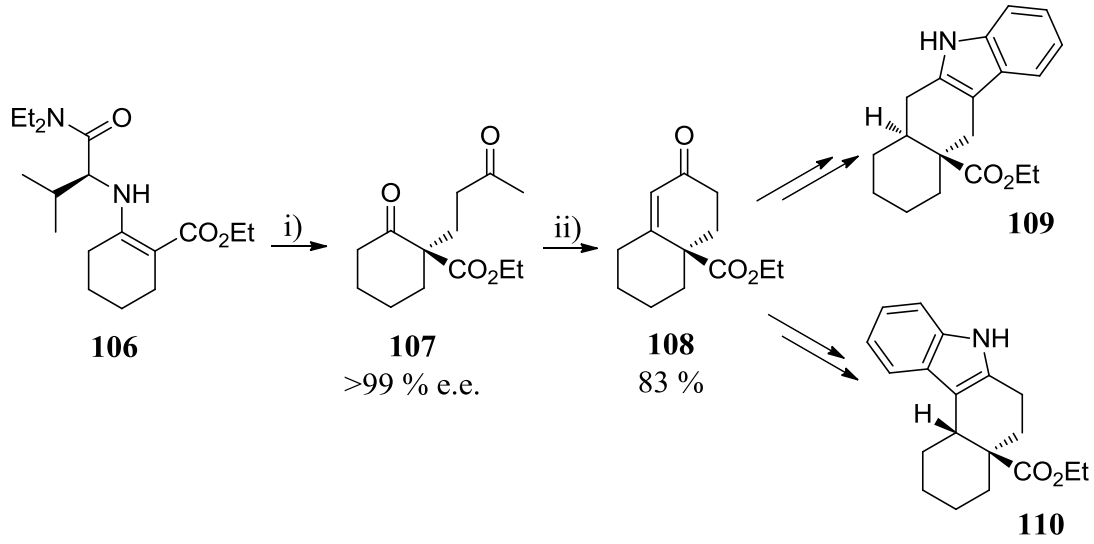
In addition to the one-pot annulation procedure, the transformation has been performed in two steps, isolating the Michael adduct prior to cyclisation. This approach has allowed stereochemical control to be applied at either stage. In the synthesis of Saudin,[80] a chiral enamine **103** was formed to direct the Michael addition, before the cyclisation step took place, giving the 6-membered ring **105** in 87 % yield and 95 % e.e. (Scheme 16).



Reagents and conditions: i) a) EVK, toluene, 50 ºC; b) aq HCl; ii) pyrrolidine, AcOH, toluene

Scheme 16: Stereoselective Michael addition and annulation in the synthesis of Saudin[80]

Christoffers *et al.* also carried out work on asymmetric copper-catalysed Michael additions, where the products can then be cyclised in a Robinson annulation. In work similar to the approach used in the synthesis of Saudin, chiral amines were investigated to direct the Michael addition, giving chiral products in modest to good enantioselectivity.[81] The conditions were then applied in the synthesis of indoles (Scheme 17).[82]

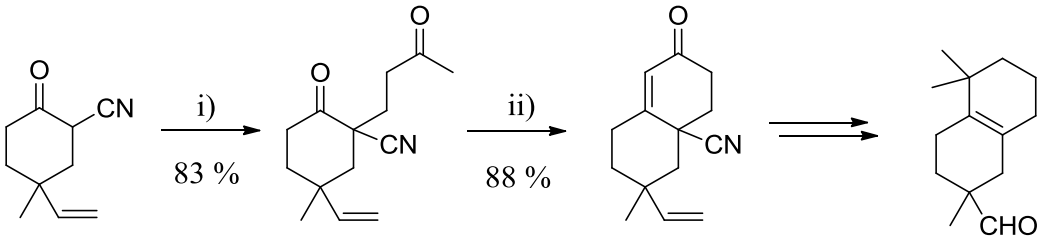


Reagents and conditions: i) a) $Cu(OAc)_2 \cdot H_2O$, MVK, acetone, 23 ºC; b) HCl/H_2O; ii) Pyrrolidine/AcOH

Scheme 17: Christoffers' application of his copper-catalysed, stereoselective Michael addition and Robinson annulation in the synthesis of indoles.[82]

The mechanism, scope and limitations and some applications of chiral imines and enamines in the asymmetric Michael addition have been reviewed by d'Angelo.[83]

Once the chiral Michael adduct has been synthesised, there are a number of methods reported in the literature for promoting the cyclisation. The use of *p*-TsOH in toluene heated at reflux was reported by Liu *et al.* to induce the annulation of ketone **112** to afford enone **113** (Scheme 18).[84]

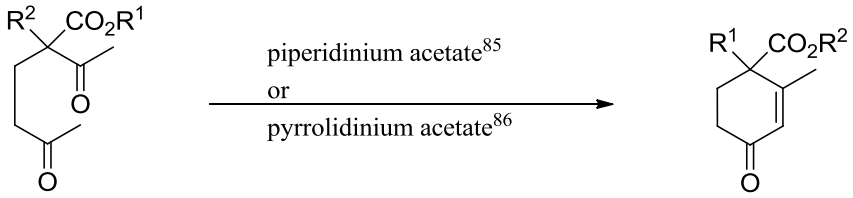


111 **112** **113** **114**
Nanaimoal

Reagents and conditions: i) DABCO, MVK, DMF, 0 ºC to r.t., 23 hrs; ii) *p*-TsOH, toluene, reflux, 24 hrs.

Scheme 18: Liu's *p*-TsOH catalysed cyclisation of Michael adduct 112 in the synthesis of nanaimoal[84]

As shown in the examples of the enamine catalysed Michael addition, pyrrolidine and piperidine can also be used to perform the annulation. In 1956, Plieninger *et al.* demonstrated that enone **116** could be formed by the cyclisation of Michael adduct **115** using piperidinium acetate.[85] Golding *et al.* developed the conditions in 1972 when synthesising Hagemann's ester **118** from **117** using pyrrolidine and acetic acid (Scheme 19).[86]



115: R^1 = Et, R^2 = Me
117: R^1 = Et, R^2 = H

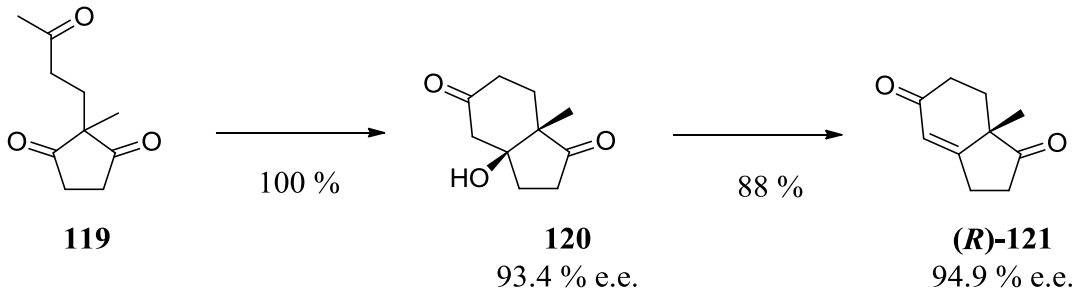
116: R^1 = Et, R^2 = Me
118: R^1 = Et, R^2 = H
(Hagemann's ester)

Scheme 19: Cyclisation of Michael adducts using piperidinium acetate or pyrrolidinium acetate

The method has since been used in the synthesis of a number of natural products or medicinally active compounds, including Saudin,[80] Hagemann's ester **118** [87] and fluorenones.[88]

Related to these conditions is the Hajos-Parrish-Eder-Sauer-Wiechert (HPESW) reaction, a stereoselective variant of the Robinson annulation which used a proline catalyst to promote the cyclisation of a pro-chiral triketone **119** to give a

chiral bicyclic product **121** (Scheme 20). The reaction was described almost simultaneously by Eder, Sauer and Wiechert in 1971[89] and by Hajos and Parrish in 1974.[90]



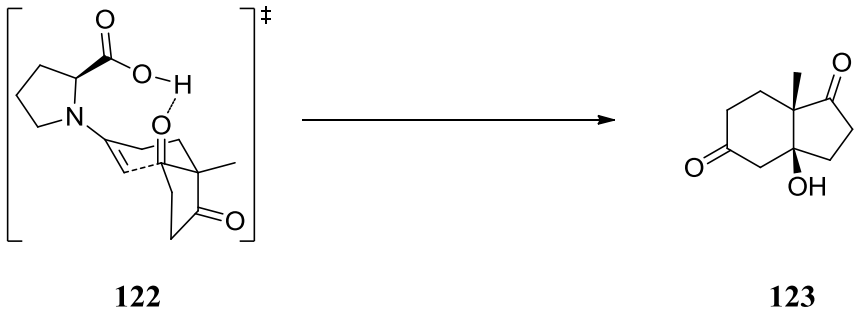
119 **120** **(*R*)-121**

93.4 % e.e. 94.9 % e.e.

Reagents and conditions: i) (*S*)-Proline, DMF; ii) *p*-TsOH, benzene, reflux

Scheme 20: Hajos-Parrish's cyclisation of triketone 119 using a proline catalyst[90]

The mechanism for the reaction has attracted much debate, with at least four different models of the transition state in the reaction. However, the widely accepted explanation for the stereoselectivity was proposed by Houk *et al.* after examining experimental evidence and computational modelling.[91]

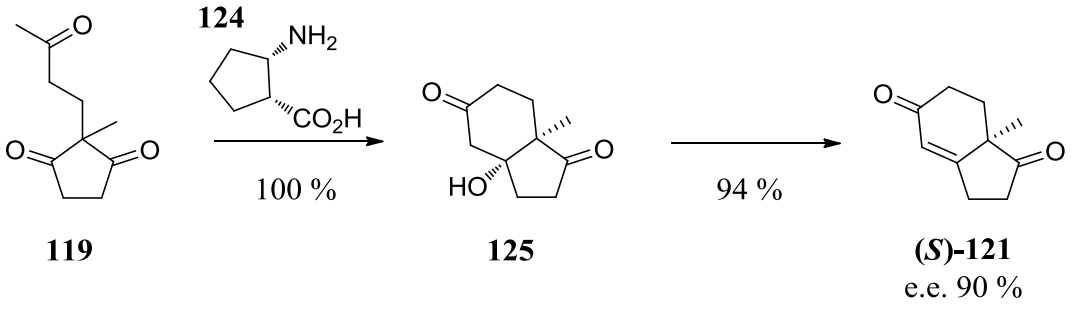


122 **123**

Figure 24: Houk's transition state model for the stereoselectivity in the annulation[91]

The use of amino acid catalysts for this reaction has been briefly reviewed by Jarvo and Miller.[92] Other amino acids have been investigated for the catalysis of this reaction. Phenylalanine[93,94,95] and proline derivatives containing substitution on the heterocyclic ring[91,96] have also been employed for the cyclisation of a range of substrates. Davies *et al.* have investigated β-amino acids as chiral catalysts for the

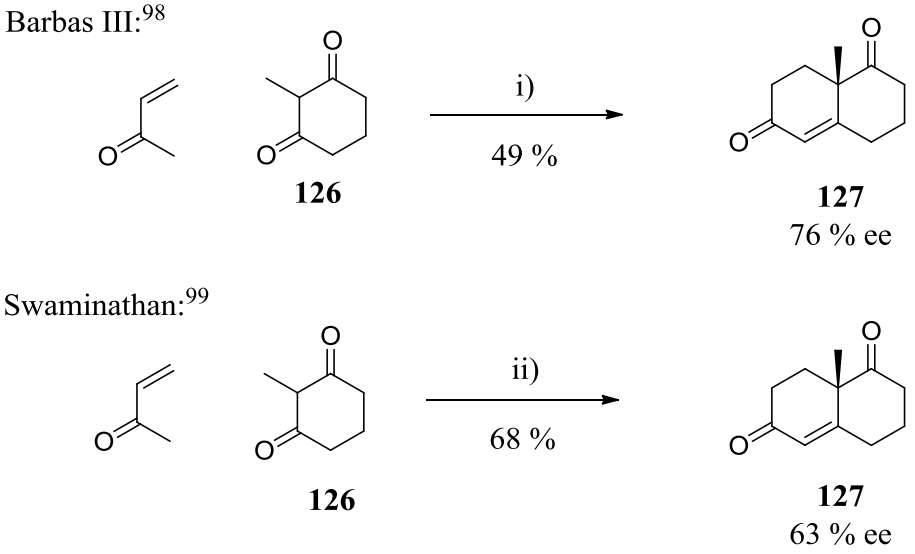
transformation and found that (1*R*,2*S*)-cispentacin **124** catalysed the HPESW reaction with comparable or higher enantioselectivity to (*S*)-proline.[97]



Reagents and conditions: i) 30 mol % **124**, DMF. r.t. ii) *p*-TsOH, toluene, reflux

Scheme 21: Davies' use of (1*R*,2*S*)-cispentacin 124 to catalyse the cyclisation of (*S*)-121.[97]

There have also been efforts to access bicyclic ketones by performing the Michael addition and aldol cyclisation in one step using proline catalysis. Barbas III *et al.* found that using (*S*)-proline in DMSO, ketone **127** can be synthesised in 49 % yield and 76 % e.e. (Scheme 22). [98] This research prompted Swaminathan *et al.* to publish their work on the same substrate, where **127** was isolated after a separate dehydration step in 68 % yield and 63 % e.e..[99]



Reagents and conditions: i) (*S*)-Proline, DMSO, 89 hrs; ii) a) (*S*)-Proline, DMSO, 145 hrs, b) *p*-TsOH, benzene, reflux.

Scheme 22: One-step synthesis of 127 using (*S*)-proline catalysis

This literature provides the basis for the work in this project on the Robinson annulation, showing the route to be viable. Although the synthesis will initially be performed racemically, these reports show that a stereoselective synthesis may also be achieved.

1.5. AIMS

The aim of this project is to synthesise simplified analogues of narciclasine, via a late stage intermediate, which retain biological activity, using a short synthetic sequence that can be applied on a larger scale.

Initially, a series of simplified AB-ring analogues will be generated to develop the conditions for the Curtius rearrangement and intramolecular Friedel-Crafts acylation. These compounds will also be tested for their anti-cancer activity.

Then a route to the ABC-ring analogues will be developed, which will use a Robinson annulation to generate the C-ring and incorporate the Curtius rearrangement and intramolecular Friedel-Crafts acylation reaction optimised on the AB-ring analogues. This route will be used to produce a series of ABC-ring analogues which will also be evaluated for their biological activity in cancer cell lines.

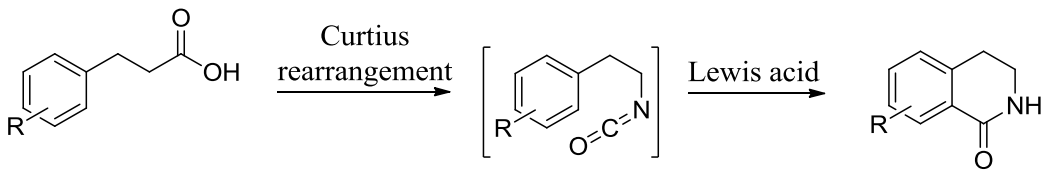
The theme of the group is the efficient synthesis of biologically active compounds using known and new methodologies. In view of this, interesting or unexpected results will also be investigated with the aim of developing new reactions that will be useful to the synthetic and medicinal chemist.

2. SYNTHESIS AND EVALUATION OF AB-RING ANALOGUES

2.1. SYNTHESIS OF AB-RING ANALOGUES USING THE CURTIUS REARRANGEMENT

2.1.1. 3,4-Dihydroisoquinolin-1-ones

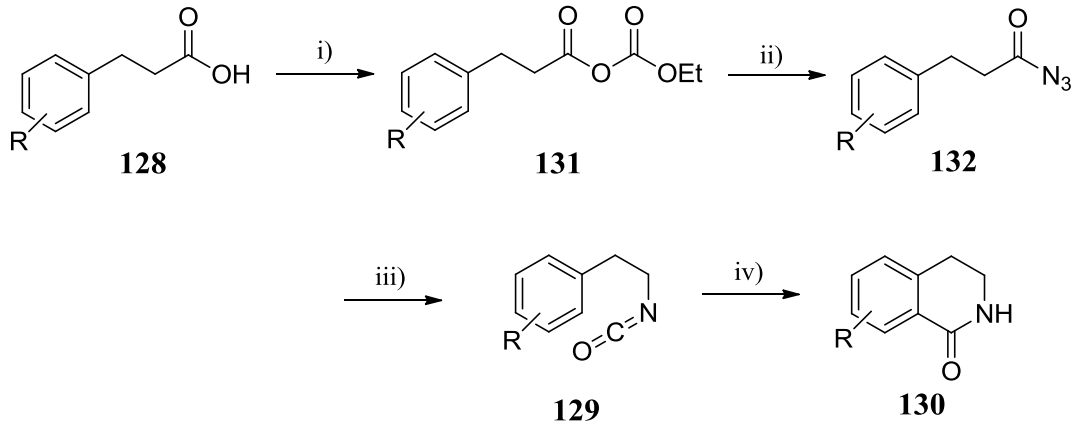
Narciclasine and pancratistatin contain a 3,4-dihydroisoquinolinone as their AB-ring. As previously discussed in Section 1.2 (p. 20), it was envisaged that this motif would be formed in a one-pot procedure from a dihydrocinnamic acid **128** through a Curtius rearrangement to generate an isocyanate **129**, followed by a Lewis acid mediated intramolecular Friedel-Crafts acylation (Scheme 23)



128 **129** **130**

Scheme 23: Dihydroisoquinolinone formation via the isocyanate

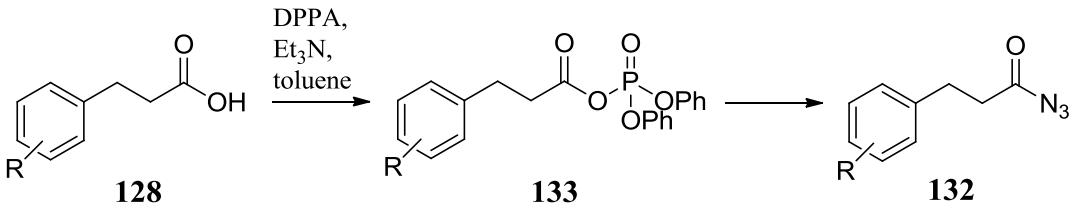
Two different methods were investigated for the Curtius rearrangement. Following the step-wise procedure reported by Ohta and Kimoto,[53] the hydrocinnamic acid was first treated with ethyl chloroformate in the presence of a base to generate the corresponding mixed anhydride **131**, which upon reaction with sodium azide afforded the acyl azide **132**. The by-products were removed by extraction and heated in toluene to afford the isocyanate **129**, then a Lewis acid was added to promote the cyclisation to give the lactam **130**.



Reagents and conditions: i) EtOCOCl, Et_3N, acetone/H_2O; ii) NaN_3; iii) heat; iv) Lewis acid

Scheme 24: Step-wise method of making an isocyanate using EtOCOCl to activate the acid

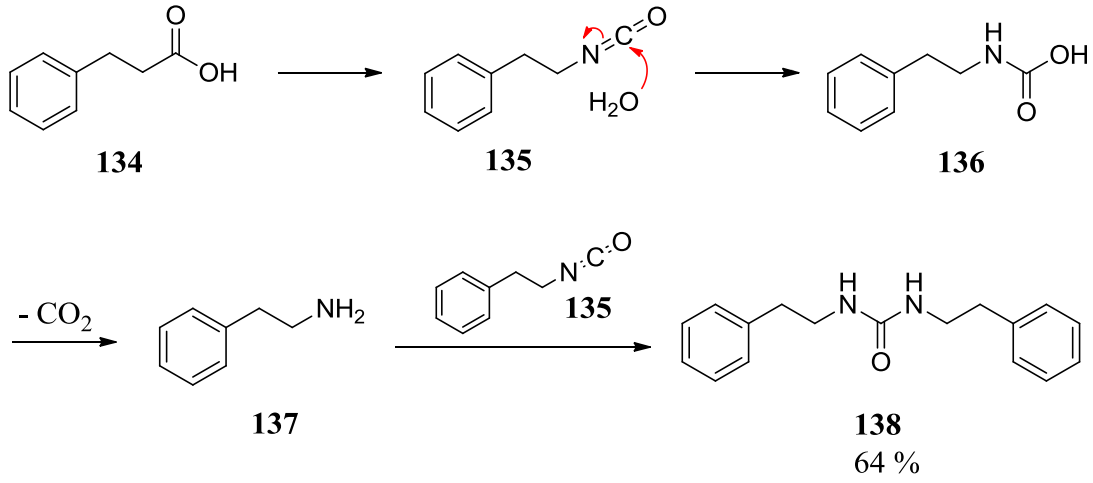
Diphenylphosphoryl azide (DPPA) was also used to generate the isocyanate in a one-pot procedure. This is a dual functional reagent, comprising of a phosphoryl group to activate the acid as the phosphoryl ester **133** and the azide group to make the acyl azide precursor **132** for the Curtius rearrangement (Scheme 25).[54] The acid **128** was heated with DPPA at 90 °C for 1 hr before the solvent was removed and the isocyanate **129** treated with a Lewis acid to furnish the isoquinolinone **130**.



Scheme 25: Mechanism for DPPA mediated azide formation

When hydrocinnamic acid **134** was treated with DPPA and Et_3N in toluene at 90 °C without the addition of a Lewis acid, the desired cyclised material was not observed; instead the symmetrical urea **138** was isolated in a 64 % yield (Scheme 26). The mechanism for urea formation involves a molecule of water. The isocyanate is hydrolysed to give the carbamic acid **136** which undergoes decarboxylation to furnish amine **137.** The urea **138** is then generated by nucleophilic addition of the amine to isocyanate **135**. However, it is not known whether this was formed in the

reaction or upon aqueous workup as the reaction was performed under anhydrous conditions.



Scheme 26: Mechanism of urea formation

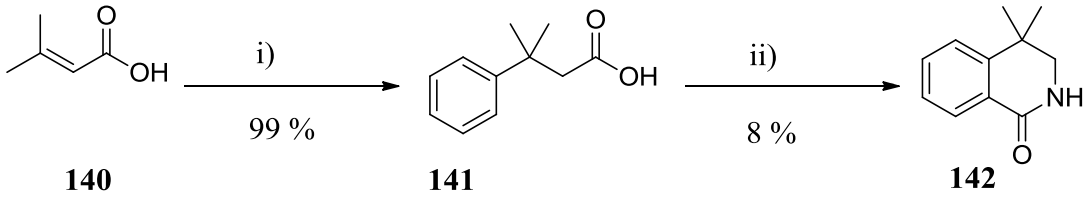
However, the formation of the urea **138** demonstrates that the isocyanate is formed during the reaction and that the subsequent ring closing step proves to be problematic. Addition of Lewis acids $BF_3 \cdot OEt_2$, $AlCl_3$ and $ZnCl_2$ were investigated to promote cyclisation; however, these gave either the urea or a mixture of compounds which could not be separated by column chromatography. It was found that increasing the temperature of the $BF_3 \cdot OEt_2$ mediated step to 80 °C promoted some cyclisation; however, the dihydroisoquinolinone **139** was isolated in only 5 % yield (Scheme 27).

Reagents and conditions: a) DPPA, Et_3N, toluene, 90 ºC; b) $BF_3 \cdot OEt_2$; c) 2M NaOH/EtOAc, 60 ºC

Scheme 27: Cyclisation of dihydrocinnamic acid 134

It was shown that the Thorpe-Ingold effect can have a positive effect on the

outcome of the reaction. The Thorpe-Ingold effect is the increase in the rate of a ring-forming reaction due the presence of substituents on the ring.[100] Using an $AlCl_3$-catalysed Michael addition of benzene to 3-methylbut-2-enoic acid **140,** 3,3-dimethyl-3-phenylpropionic acid **141** was synthesised in 99 % yield. The acid was then subjected to the stepwise reaction conditions, performing the $BF_3{\cdot}OEt_2$ mediated cyclisation at room temperature, to give the 4,4-dimethylisoquinolinone **142** in 8 % yield (Scheme 28).



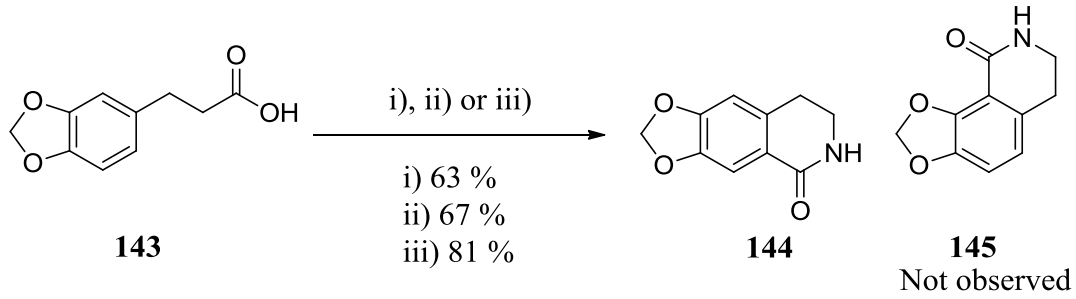
140 **141** **142**

Reagents and conditions: i) $AlCl_3$, benzene; ii) a) EtOCOCl, Et_3N, acetone/H_2O; b) NaN_3, acetone/H_2O; c) toluene, 90 °C; d) $BF_3{\cdot}OEt_2$

Scheme 28: The Thorpe-Ingold effect increases the rate of cyclisation

An unsubstituted aryl group is a poor nucleophile due to the lack of electron-donating substituents on the ring. Substrates with electron-rich, oxygenated aryl rings were investigated as they would be better nucleophiles and because narciclasine contains an oxygenated A-ring

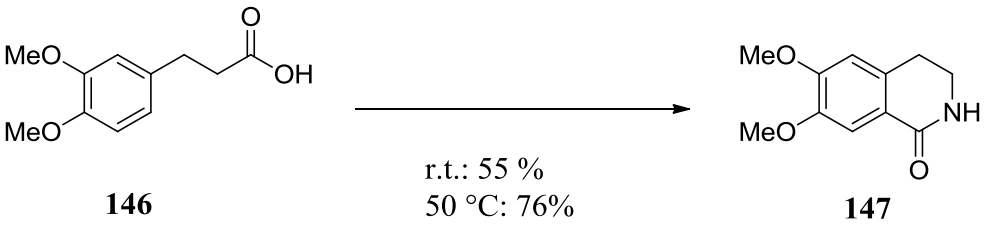
3-(3,4-Methylenedioxyphenyl)propionic acid **143** was subjected to three different sets of conditions for the rearrangement and cyclisation. When the step-wise conditions were applied and $BF_3{\cdot}OEt_2$ was used to promote the cyclisation, the isoquinolinone **144** was isolated in 63 % yield. Using the step-wise conditions and $AlCl_3$ as the Lewis acid afforded **144** in 67 % yield. When the reaction was performed using DPPA the lactam **144** was isolated in 81% yield (Scheme 29). Only regioisomer **144** was formed in the reactions and isomer **145** was not observed. This was proved with the ^1H NMR spectra where the aromatic region contained only two singlets at 6.64 ppm and 7.49 ppm. Two doublets with a coupling constant of around 8 Hz would be expected for regioisomer **145**.



Reagents and conditions: i) a) EtOCOCl, Et_3N, acetone/H_2O; b) NaN_3, acetone/H_2O; c) toluene, 90 °C; d) $BF_3{\cdot}OEt_2$; ii) a) EtOCOCl, Et_3N, acetone/H_2O; b) NaN_3, acetone/H_2O; c) toluene, 90 °C; d) $AlCl_3$; iii) a) DPPA, Et_3N, toluene, 90 °C; b) $BF_3{\cdot}OEt_2$; c) 2M NaOH, EtOAc, 50 °C.

Scheme 29: Cyclisation of 3-(3,4-methylenedioxyphenyl)propionic acid 143

3,4-(Dimethoxyphenyl)propionic acid **146** was also investigated as a substrate for the reaction; however using the DPPA reaction conditions, lactam **147** was isolated in only 55 % yield. Heating the $BF_3{\cdot}OEt_2$ mediated cyclisation step at 50 °C increased the yield to 76 % (Scheme 30).



Reagents and conditions: a) DPPA, Et_3N, toluene, 90 °C; b) $BF_3{\cdot}OEt_2$, r.t. or 50 °C; c) 2 M NaOH, EtOAc, 50 °C.

Scheme 30: Cyclisation of 3-(3,4-methylenedioxyphenyl)propionic acid 146

As narciclasine contains a trioxygenated A ring, the cyclisation of (3,4,5-trimethoxyphenyl)propionic acid **148** was investigated. When the acid was submitted to the step-wise set of conditions, using $BF_3{\cdot}OEt_2$ as the Lewis acid, the ^1H NMR spectrum of the product showed the loss of a methyl group, however the site of demethylation could not be determined. Regioselective demethylation by $BF_3{\cdot}OEt_2$ has been reported in similar systems and was discussed in Section 1.3 (p. 26).[70] As the product was a thermally stable and highly crystalline solid, an X-ray crystal structure was obtained to determine the site of demethylation (Figure 25).

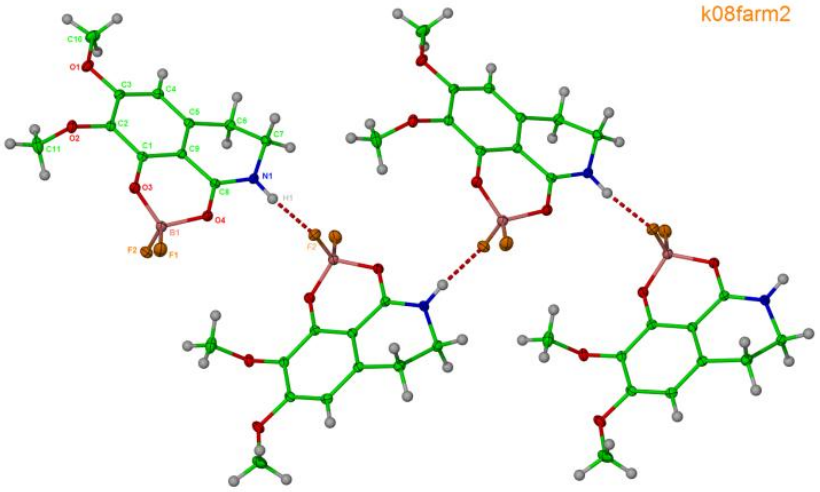
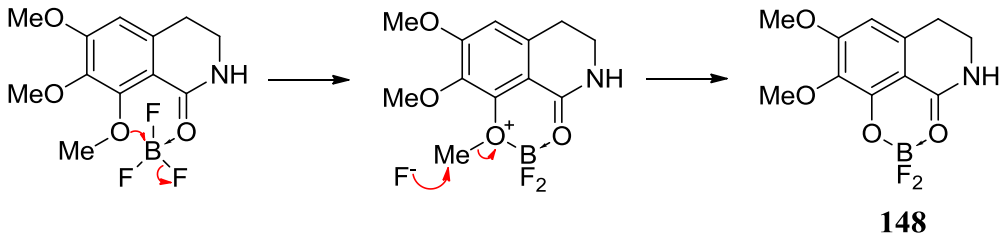


Figure 25: Crystal structure of demethylated compound 148, coordinated with boron difluoride

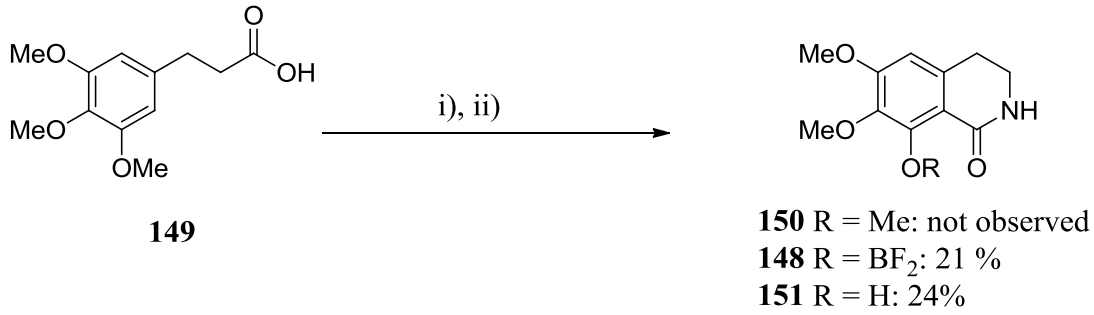
The structure shows the demethylated product coordinated to boron difluoride through the phenol and carbonyl groups. Presumably, as the boron trifluoride coordinates to the product, there is loss of a fluoride ion which can act as a nucleophile to perform the demethylation, allowing the resulting phenol to bind more strongly to the boron to give the thermally stable adduct **148** (Scheme 31).



148

Scheme 31: Proposed mechanism of selective demethylation of the 8-methoxy group

The trimethoxy-product **150** was not observed and the BF_2-adduct was isolated in an unoptimised 21 % yield (Scheme 32). Nicolau *et al.* reported similar chelate structures and described their hydrolysis using refluxing methanol/water or THF/water.[101] The dissociation of **148** was achieved using 2M NaOH and EtOAc at 50 °C and the free phenol **151** was isolated in an unoptimised 24 % yield from the propionic acid **149**.



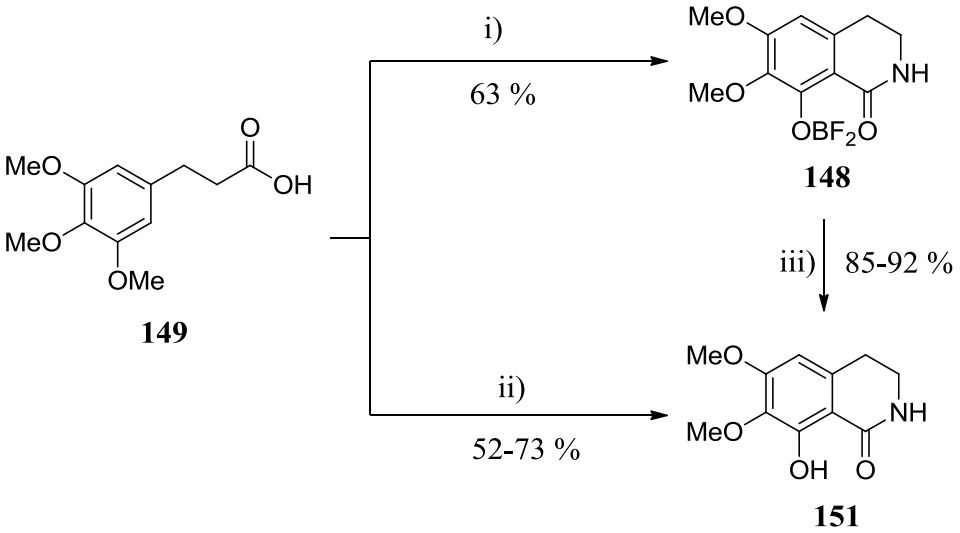
149

150 R = Me: not observed
148 R = BF_2: 21 %
151 R = H: 24%

Reagents and conditions: i) a) EtOCOCl, Et_3N, acetone/H_2O; b) NaN_3, acetone/H_2O; c) toluene, 90 °C; d) $BF_3{\cdot}OEt_2$; ii) 2M NaOH, EtOAc, 50 ºC (**151** only)

Scheme 32: Cyclisation and demethylation of 3-(3,4,5-trimethoxyphenyl)propionic acid 149 using the unoptimised stepwise procedure

When the rearrangement and cyclisation of (3,4,5-trimethoxyphenyl)propionic acid **149** was attempted using DPPA, lactam **151** was isolated in 73 % yield on a 5 mmol scale, but only in 52 % yield on a 25 mmol scale. After optimisation, the BF_2-adduct **148** could be isolated in 62 % yield on a 25 mmol scale without column chromatography. Subsequent hydrolysis was performed using 2M NaOH and EtOAc, giving lactam **151** in an 85-92 % yield on a 5 mmol scale.



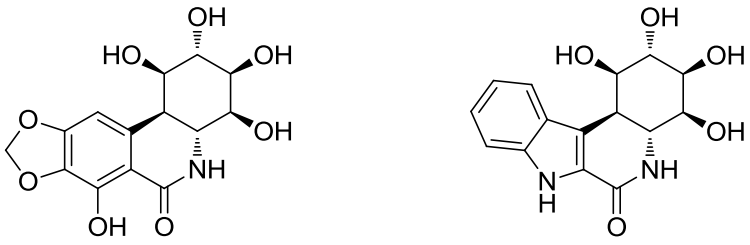
149

Reagents and conditions: i) a) DPPA, Et_3N, toluene, 90 ºC; b) $BF_3{\cdot}OEt_2$; ii) a) DPPA, Et_3N, toluene, 90 ºC; b) $BF_3{\cdot}OEt_2$; c) 2M NaOH, EtOAc, 50 ºC; iii) 2M NaOH, EtOAc, 50 ºC.

Scheme 33: Synthesis of 8,9-dimethoxy-7-hydroxy-3,4-dihydroisoquinolinone 151

2.1.2. Indole Analogues

Hudlicky *et al.* proposed that in pancratistatin the A-ring could be substituted for an indole where the NH mimics the hydroxyl group.[26] Indole is an electron rich aromatic ring that can capture an isocyanate, as demonstrated by Hilton *et al.*,[69] a range of indole carboxylic acids were investigated as substrates for the reaction.

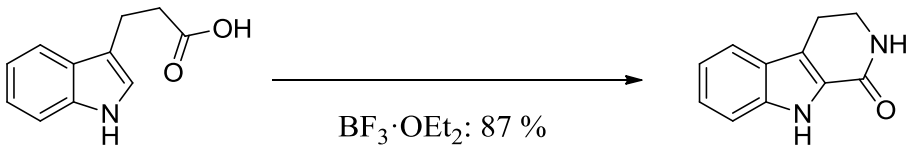


Pancratistatin
7

Hudlicky's analogue
9

Figure 26: Pancratistatin 7 and Hudlicky's indole analogue 9

Indole-3-propionic acid **152** was treated with DPPA and Et_3N in toluene at 90 °C, followed by cyclisation mediated by $BF_3{\cdot}OEt_2$ to afford carbolinone **153** in 87 % yield which is a natural product isolated from an Indonesian sponge.[102] When $AlCl_3$ was employed as the Lewis acid, the lactam was isolated in **153** in 79 % (Scheme 34).



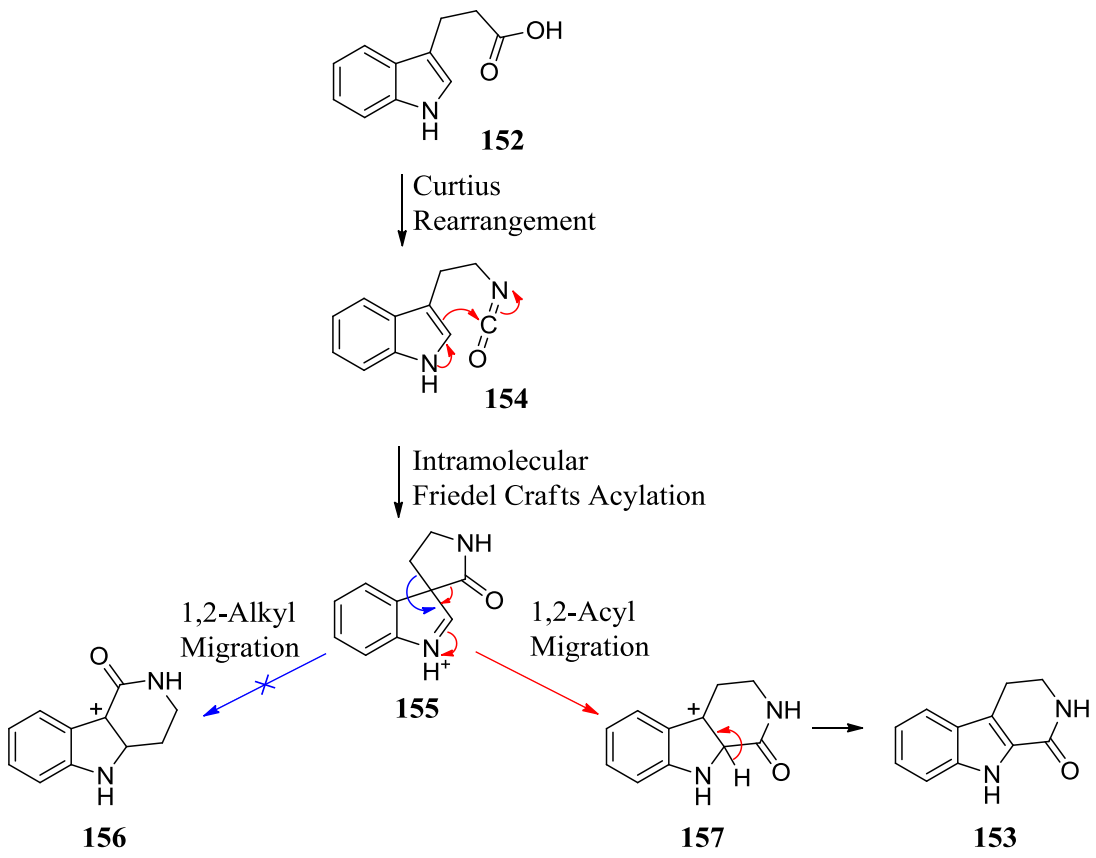
152 **153**

Reagents and conditions: a) DPPA, Et_3N, toluene, 90 °C; b) $BF_3{\cdot}OEt_2$ or $AlCl_3$.

Scheme 34: Cyclisation of indole-3-propionic acid 152

The mechanism for the Curtius rearrangement is the same as that for the oxygenated aryl ring analogues. However, the cyclisation step proceeds with more complexity due to the electronics of the indole ring (Scheme 35). In indole, the lone pair on the nitrogen atom is involved in the aromaticity of the ring, so can be

delocalised onto the 3-position, making this the most nucleophilic position within the ring. This means that the isocyanate is trapped by the 3-position to give a spirocyclic intermediate **155**, which must undergo a migration and deprotonation to restore aromaticity to the indole. This spirocyclic intermediate has been described previously in related systems with substitution at the 2-position, which prevented migration and allowed the compounds to be isolated and characterised.[103] Only a 1,2-acyl migration was observed, the product of a 1,2-alkyl migration was never isolated. This is because as the group migrates, a positive charge develops at the 3-position and this will be affected by the remaining adjacent group. An adjacent acyl group is electron withdrawing so would destabilise the cation, whereas an adjacent alkyl group is slightly electron-donating so will act to stabilise the positive charge. This leads to migration of the acyl group, giving carbolinone **153** as the product.



Scheme 35: Mechanism for the cyclisation of indole-carboxylic acids

The structure was determined by 2D ^{1}H NMR experiments and X-ray crystallography, where the N-H and carbonyl can be seen on the same side of the

molecule, indicating a 1,2-acyl migration. The crystal structure also showed the ribbon-like arrangement of molecules formed by hydrogen bonding.

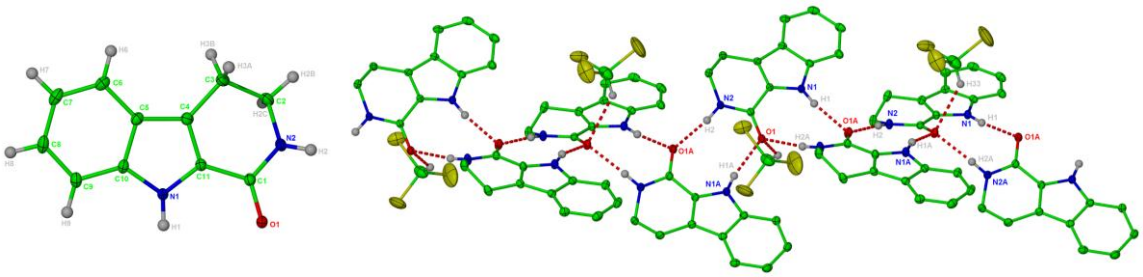
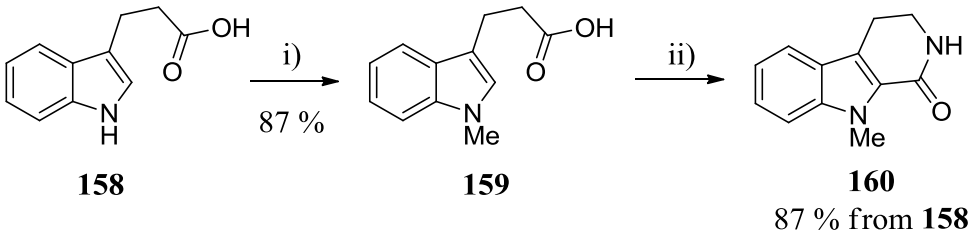


Figure 27: X-ray crystal structures of carbolinone 153

The *N*-methylated analogues were also synthesised. Following the methylation procedure reported by Compernolle using iodomethane in the presence of KOH, followed by base hydrolysis of the ester, *N*-methylindole-3-propionic acid **159** was synthesised in 87 % yield (Scheme 36).[104] The acid **159** was then subjected to the optimised reaction conditions to afford the carbolinone in 87 % from indole-3-propionic acid **160.**

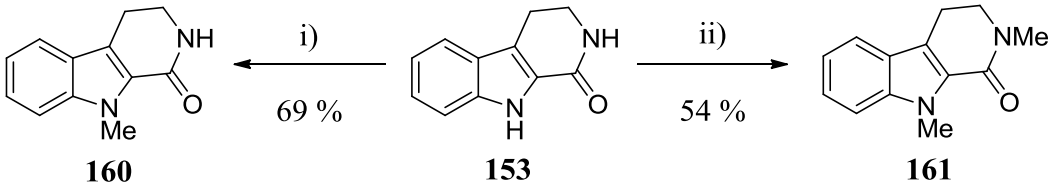


158 **159** **160**
87 % from **158**

Reagents and conditions: i) a) MeI, KOH, acetone; b) KOH, water reflux; ii) a) DPPA, Et_3N, toluene, 90 °C; b) $BF_3 \cdot OEt_2$; c) 2M NaOH, EtOAc, 50 °C.

Scheme 36: Synthesis of methylated carbolinone 160

The *N*,*N*-dimethylcarbolinone **160** was synthesised by methylation of carbolinone **153**. Using iodomethane and KOH as described by Compernolle resulted in the methylation of only the indole to give **160** in 69 % yield, whereas the use of NaH as the base as reported by Hamann[105] gave the dimethyl-analogue **161** in 55 % yield (Scheme 37).



160 **153** **161**

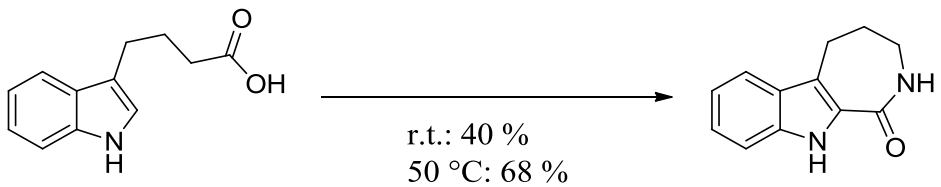
Reagents and conditions: i) MeI, KOH, acetone; ii) MeI, NaH, THF.

Scheme 37: Methylation of carbolinone 153

Other chain lengths linking the indole and the carboxylic acid were also investigated. When the reaction conditions were applied to indole-3-carboxylic acid and indole-3-acetic acid, mixtures of products inseparable by column chromatography were observed. This is possibly due to the mechanism of the reaction, where the substrates must proceed via 3- and 4- membered ring spirocyclic structures, which are thermodynamically unfavourable.

Azepinones are 7-membered ring homologues of the carbolinones and have been shown to be interesting as anti-mitotic compounds which inhibit tubulin polymerisation by Dodd *et al.*[106] and Joseph *et al.*[107]

The commercially available indole-3-butyric acid **162** was submitted to the optimised cyclisation conditions and the product **163** was isolated in only 40 % yield (Scheme 38). The yield was increased to 68 % and 90 % when the $BF_3{\cdot}OEt_2$ mediated cyclisation was performed at 50 °C and 80 °C respectively. Presumably, the elevated temperatures aid the energetically unfavourable ring expansion from the 6-membered spirolactam to the 7- membered azepinone.

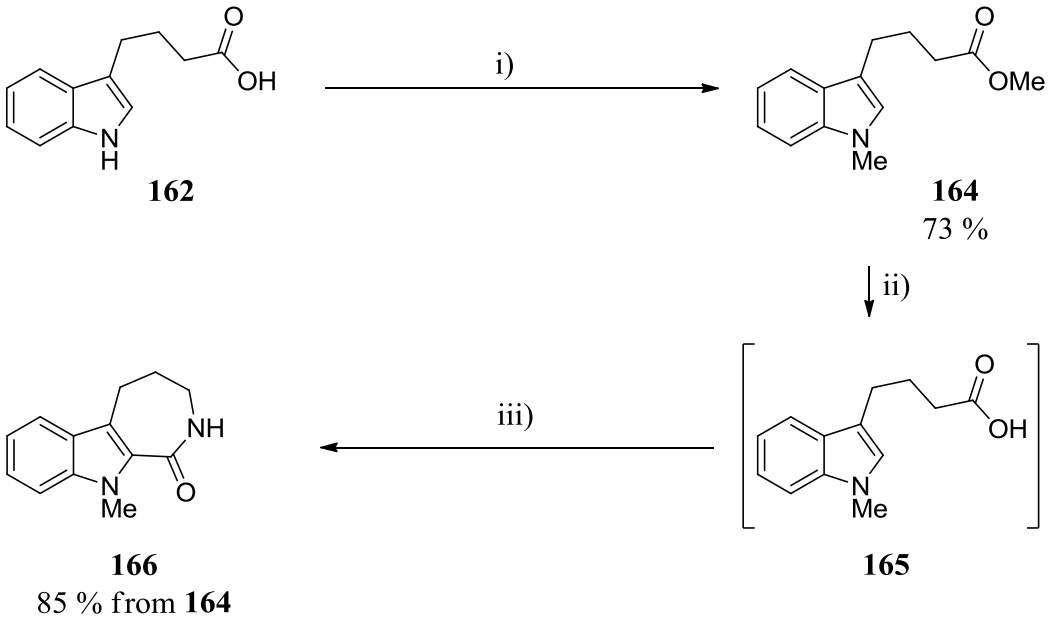


162 **163**

Reagents and conditions: a) DPPA, Et_3N, toluene, 90 °C; b) $BF_3{\cdot}OEt_2$; c) 2M NaOH, EtOAc, 50 °C.

Scheme 38: Cyclisation of indole-3-butyric acid 162

The methylated derivatives were also synthesised to probe the role of the acidic protons in the molecule. Surprisingly, when indole-3-butyric acid **162** was subjected to the conditions previously used for the methylation of indole-3-propionic acid **152** as reported by Compernolle,[104] only the starting material was recovered. However, methylation of the indole nitrogen and the ester was achieved using *t*-BuOK and iodomethane in DMF as reported by Perregaard, to give ester **164** in 73 % yield.[108] The ester was then hydrolysed in aqueous KOH to provide the crude acid **165** which was cyclised at 50 °C to give **166** in 85 % yield from the ester **164** (Scheme 39).

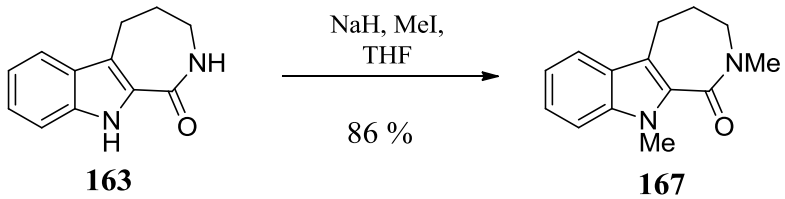


162 **164** 73 % **165** **166** 85 % from **164**

Reagents and conditions: i) a) *t*-BuOK, DMF, 5 mins; b) MeI, 16 hrs; ii) KOH, H_2O; iii) a) DPPA, Et_3N, toluene, 90 °C; b) $BF_3 \cdot OEt_2$, 50 °C; c) 2M NaOH/EtOAc, 50 °C.

Scheme 39: Synthesis of mono-methylated azepinone derivative 166

The dimethylated analogue **167** was also synthesised in 86 % yield by the dimethylation of azepinone **163** using NaH and iodomethane in THF (Scheme 40).



163 **167**

Scheme 40: Methylation of azepinone 163

2.2. SYNTHESIS OF AB-RING ANALOGUES BY THE DEHYDROGENATION OF LACTAMS

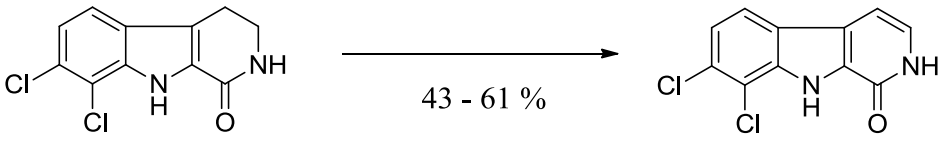
2.2.1. Dehydrogenation of Lactams using DDQ

To emulate the sp^2 centre at the 10b position of narciclasine, the oxidation of the previously synthesised AB-ring analogues was investigated. There are a number of reported methods of performing the oxidation and one of the approaches that was explored was the use of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ).

Chang *et. al.*[110]

168 **169**

Bracher *et. al.*[111] and Islam *et. al.*[112]

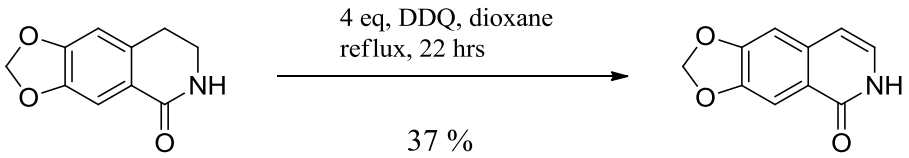


170 Bauerine C **171**

Reagents and conditions: i) DDQ, THF or dioxane, reflux.

Scheme 41: Examples of DDQ mediated dehydrogenation

DDQ has been described extensively in the literature for performing dehydrogenations at benzylic positions and a review of its reactions was published in 1967.[109] Since then, DDQ in dioxane or THF heated at reflux has been reported for the oxidation of dihydroisoquinolinones **168**;[110] in the synthesis of Bauerines A, B and C **171** [111,112] and in the synthesis of carbolines[113] (Scheme 41).

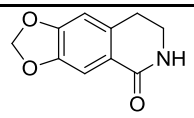
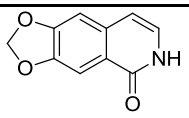
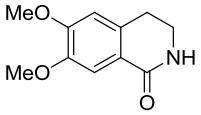
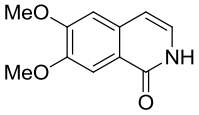
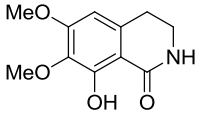
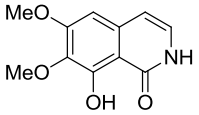
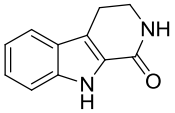
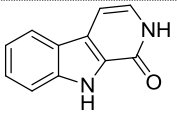
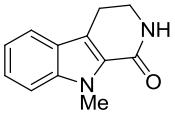
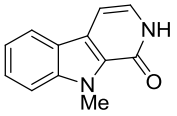


144 **172**

Scheme 42: Dehydrogenation of 144 using DDQ

Following the literature precedent, the methylenedioxy-derivative **144** was treated with 4 eq. DDQ in dioxane heated at reflux (Scheme 42). After 4 hrs, ^{1}H NMR analysis of the crude material showed a 2:1 mixture of starting material to product **172**. Increasing the reaction time to 22 hrs increased the conversion to 75 % by ^{1}H NMR; however, the isolated yield of **172** was only 37 % (Table 1, entry 1). Portion-wise addition of DDQ to the reaction mixture did not increase the yield and isoquinolinone **172** was isolated in only 31 % yield after the addition of 4 eq. DDQ in three portions over 32 hrs.

Table 1: Oxidative aromatisation of lactam rings using DDQ

Entry	Starting material	Product	eq. DDQ	Yield (%)
1	 **144**	 **172**	4	37
2	 **147**	 **173**	4	31
3	 **151**	 **174**	4	-
4	 **153**	 **175**	4 3[a]	25 58
5	 **160**	 **176**	4 3[a]	- 22

***a*: Performed using 3 eq. DDQ for 1 hr**

The remaining analogues were oxidised using 4 eq. DDQ added in one portion (Table 1). The dimethoxy derivative **173** was isolated in 31 % yield (Entry 2). When the 6,7-dimethoxy-8-hydroxy analogue **151** was subjected to the reaction conditions, full conversion was not achieved and the oxidised product **174** could not be separated from the starting material by column chromatography (Entry 3). A mixture of products resulting from the conjugate addition of the substrate to DDQ was also observed. The carbolinone **175** was isolated in 25 % yield (Entry 4); however the oxidation of *N*-methylcarbolinone **160** led to demethylation. Altering the reaction conditions to 3 eq. DDQ for only 1 hr gave the desired *N*-methylcarbolinone **176** in 20 % yield (Entry 5). These conditions were also applied to the carbolinone **153** to give the oxidised product **175** in 58 % yield (Entry 4).

The driving force for this transformation is the formation of an extended aromatic system, so unsurprisingly the azepinones could not be oxidised using these conditions and in these cases unchanged starting material was recovered.

Due to the poor yields of these reactions, alternative methods of performing the oxidation were investigated. Following literature reported by Snider,[114] and Ciganek;[115] MnO_2 and Ag_2O were briefly investigated as oxidants, however only the starting material was recovered from the reactions.

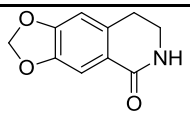
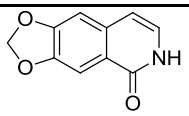
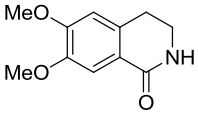
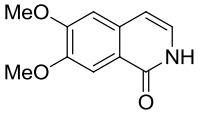
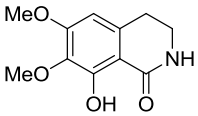
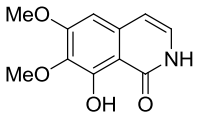
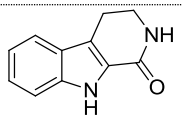
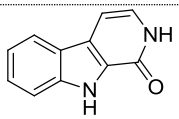
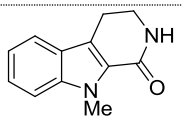
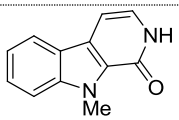
2.2.2. Dehydrogenation of Lactams using Palladium on Carbon

Palladium on carbon (Pd/C) is typically used as a hydrogen transfer agent in the presence of hydrogen gas for the reduction of double bonds, but it has also been described in the formation of double bonds in the absence of hydrogen. The oxidation of dihydroisoquinolinones has been reported by Hutchinson,[116] and Bracher described the dehydrogenation of carbolinones.[117]

Following the procedure reported by Dufour,[118] the 6,7-methylenedioxy-derivative **144** was oxidised using 7 mol% Pd/C in xylene heated at reflux and after 24 hrs, the catalyst was removed by filtration and the product **172** was isolated in 53 % yield (Table 2, entry 1a). Using the same procedure, the dimethoxy analogue **147**

was oxidised in to afford isoquinolinone **173** in 61 % yield (Entry 2a) and the 8-hydroxy derivative **174** was isolated in 51 % yield (Entry 3a). Dehydrogenation of the carbolinones **153** and **160** was also achieved in 39 % in 60 % yields respectively (Entries 4 and 5).

Table 2: Dehydrogenation of lactam rings using Pd/C

Entry	Starting material	Product	Thermal yield (%)	Microwave yield (%)
1	 **144**	 **172**	54[a] 42[b] 67[c]	-
2	 **147**	 **173**	61[a] 87[c]	98[d]
3	 **151**	 **174**	51[a] 49[b] 38[c]	80
4	 **153**	 **175**	39[a]	90
5	 **160**	 **176**	60[a]	-

a: achieved using 7 mol% Pd/C and the catalyst was removed by filtration through celite.
b: achieved using 33 mol% Pd/C and the catalyst was removed by filtration through celite.
c: achieved using 15 mol% Pd/C and the catalyst was removed column chromatography.
d: performed by Gemma Tunbridge

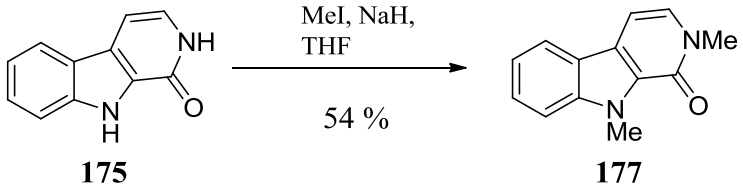
The reactions were found to be capricious and starting material was often recovered when the reactions were repeated. Increasing the amount of Pd/C used to 33 mol% did not improve the reliability or yield of the reactions. The oxidation of the 6,7-methylenedioxy derivative **144** was performed on an 8 mmol scale using 33 mol% Pd/C and the product **172** was isolated in 42 % yield (Entry 1b). Oxidation of the 8-hydroxy derivative **151** on a 5.95 mmol scale was achieved to give the product **174** in 49 % yield (Entry 3b).

^{1}H NMR analysis of the reaction mixtures showed clean conversion of the starting materials to products, implying that the poor yields were due to problems in the purification of the products. Changing the method of removing the catalyst from filtration through celite to column chromatography generally increased the yields in the reactions. Using 15 mol% Pd/C, the methylenedioxy derivative **172** was isolated in 67 % yield and the dimethoxy derivative **173** was isolated in 87 % yield (Entries 1c and 2c).

Different solvents, including EtOH, EtOAc, *t*-BuOH and AcOH, were also examined as for the dehydrogenation; however, the products were not observed and the starting materials reclaimed. Cyclohexene has been described in the literature as an additive to dehydrogenation reactions as it acts a hydrogen sink, removing the hydrogen taken from the lactam ring by its reduction to cyclohexane.[116] This had no effect on the reaction and only the starting materials were isolated.

Microwave technology has provided the greatest amount of success with these reactions, allowing temperatures of up to 200 °C to be reached and the reaction times to be reduced dramatically whilst achieving high yields. After 1 hr at 200 °C, 6,7-dimethoxy-8-hydroxyisoquinolinone **151** was oxidised to give **174** in 80 % yield; and after only ½ hr, carbolinone **175** was isolated in an 89 % yield. The reactions conditions have since been repeated within the group using the dimethoxy analogue **147**, affording **173** in an excellent yield of 98 %!

The oxidation of the *N*,*N*-dimethyl analogue **161** was not performed, however the carbolinone **177** was synthesised by methylation of carbolinone **175** using iodomethane and NaH in 54 %.



175 **177**

Scheme 43: Methylation of carbolinone 175

2.3. BIOLOGICAL EVALUATION

The compounds have all been tested in an MTS cell proliferation assay using human HT29 colon cancer cells with a 72 hr exposure time. The compounds were tested twice and an average taken.

The AB-ring analogues did not possess potent anti-cancer activity (Figure 28). In the series of dihydroisquinolinones, the methylenedioxy and dimethoxy derivatives **144** and **147** were found to be inactive and the 8-hydroxy analogue **151** displayed a weak activity of 386 μM. The series of isoquinolinones **172**, **173** and **174** were more active with IC_{50} values of 398 μM to 71 μM and the 8-hydroxy analogue **174** was the most active compound in the series. Despite the weak activity, the trends in the potency of these compounds do mirror those in the natural product discussed in Section 1.1.3 (p. 7). The presence of the 8-hydroxyl group increases the activity and the oxidation of the C4 position to an sp^2 centre also increases the activity. Interestingly, the methylenedioxy analogue **172** is less active than the dimethoxy analogue **173**, implying that the substitution pattern on the A-ring of narciclasine may not be optimal for activity.

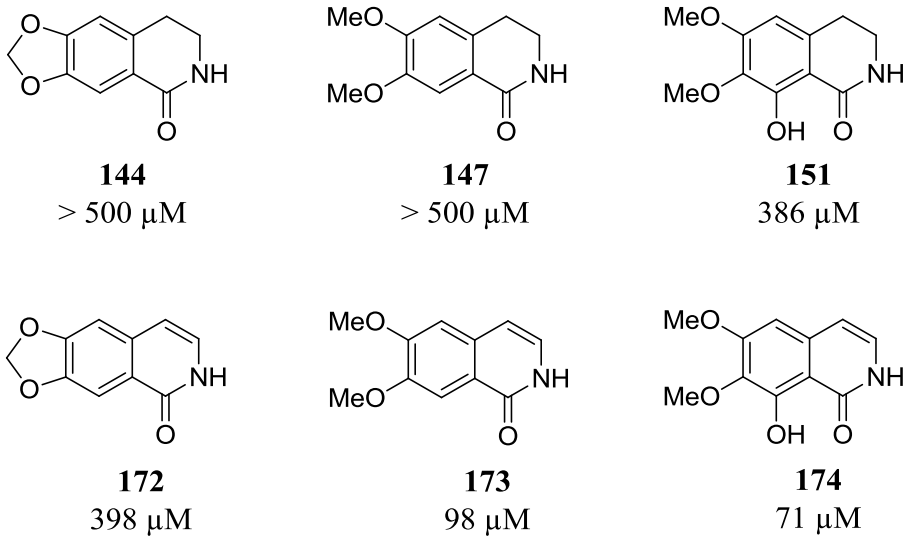
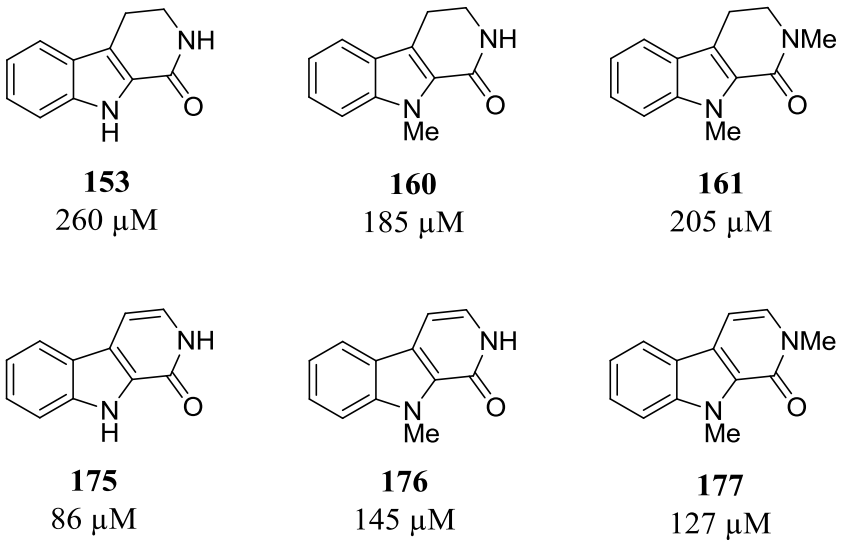


Figure 28: Biological activity of the isoquinolinones

In addition to these results, two of the compounds have biological data reported in the literature. The dimethoxy-derivative **147** shows some anti-tumour

promoting activity,[119] and its oxidised analogue **173** has been shown to be a weak inhibitor of TNF-α, a protein involved in inflammation and apoptosis.[120]

The indole analogues **153**, **160**, **161**, **175**, **176** and **177** were also found to be only mildly active in HT29 cells with IC_{50} values of 260 μM to 86 μM (Figure 29). As with the isoquinolinones, oxidation of the lactam ring increases the activity of the analogues. However, there is not a definite pattern for the effect of *N*-methylation on activity, as within the unoxidised series **153** is the least active analogue yet its oxidised **175** counterpart is the most active within its series. This may be due to the compounds having an effect at more than one target within the cell. For example, carbolinones have been found to be inhibitors of MK2,[121] a kinase involved in the inflammatory response and apoptosis.



153 260 μM | **160** 185 μM | **161** 205 μM

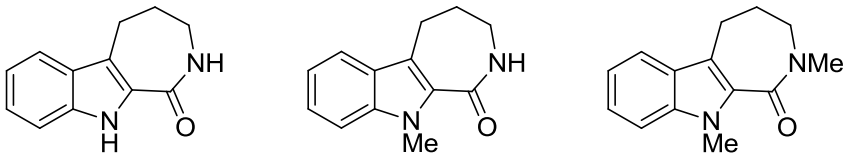
175 86 μM | **176** 145 μM | **177** 127 μM

Figure 29: Biological activity of carbolinones

In addition to Hudlicky's use of the indole moiety as a substitute for the oxygenated aryl ring in narciclasine analogues, carbolinones are interesting medicinal compounds in their own right. Carbolinone **153** has been tested for its anti-leishmaniasis activity, but was found to be inactive.[105] Its oxidised analogue **175** has been found to be inactive against HeLa cells.[122]

The azepinone analogues **163**, **166** and **167** were less active than the carbolinones, displaying activities of 120 μM, 302 μM and 373 μM respectively

(Figure 30). However, the structure-activity relationship is much easier to see; *N*-methylation drastically reduces activity implying that these protons are important for interactions with the target.



163 120 μM | **166** 302 μM | **167** 373 μM

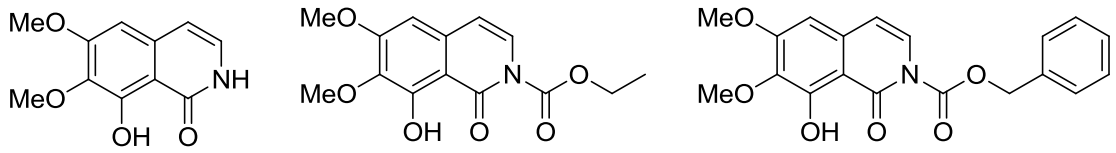
Figure 30: Biological activity of azepinones

Azepines have been described by Dodd *et al.*[106] and Joseph *et al.*[107] as inhibitors of tubulin polymerisation, so these compounds could possibly act by this mechanism either instead, or in addition to, the mechanisms by which narciclasine works. A method of investigating this would be to submit the compounds to a tubulin-binding assay, whereby the amount of tubulin polymerisation or depolymerisation is assessed by measuring changes in turbidity of the assay mixture.

2.4. SYNTHESIS OF PRO-DRUGS

As previously discussed in the introduction, narciclasine and its congeners suffer from poor solubility so pro-drugs have been synthesised to improve their *in vivo* properties. The synthesis of a series of pro-drugs was undertaken in this project to investigate if their use could improve the physical properties and activity of the AB-ring analogues. The approach taken in this project was the use of carbamates and carbonates to mask the amide and phenol groups. As shown by the X-ray crystal structure of the carbolinone **174** (Figure 27), the lactams are able to form a series of hydrogen bonds which must be broken in order to dissolve the compound. Formation of the pro-drugs removes the hydrogen bond donors, preventing the number of bonds the product can form and aiding solubility. The lipophilicity of the phenol **174** has been increased by the synthesis of its pro-drugs (Figure 31),[123] but remains below 5; the limits of Lipinski's Rules for absorption of drugs *in-vivo*.[124] Only the most active

6,7-dimethoxy-8-hydroxyisoquinolinone **174** was used in the first instance as a proof of principle.



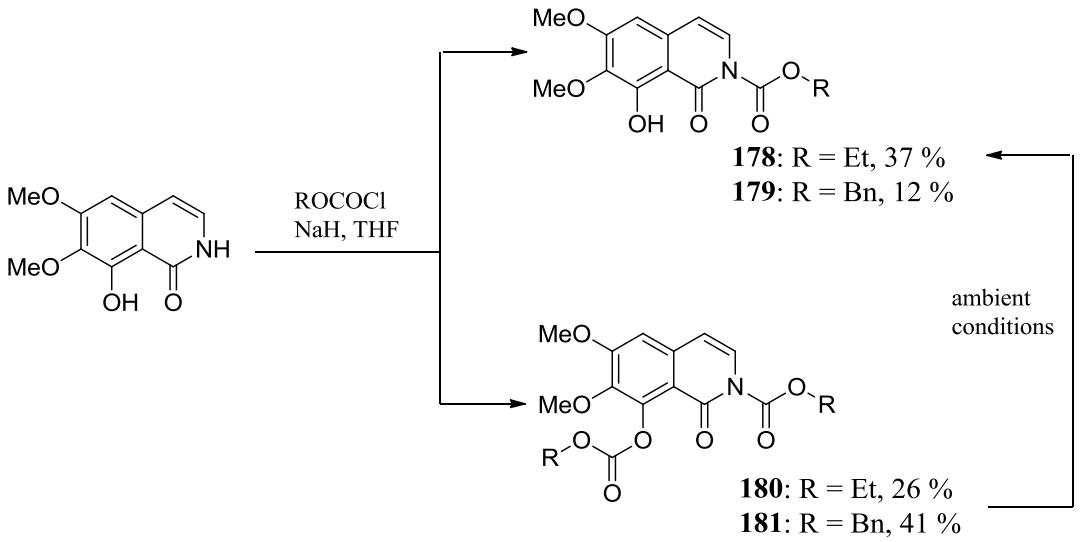
174
Log P: 0.64
CLogP: 0.282

178
Log P: 1.51
CLogP: 0.479

179
Log P: 2.91
CLogP: 1.718

Figure 31: Partition coefficients of the parent compound 174 and the pro-drugs 178 and 179

Ethyl and benzyl carbamates and carbonates were synthesised using the corresponding chloroformate and NaH in THF in 12-41 % yields (Scheme 44). The poor yields may partly be due to the instability of the carbonate. The ethyl and benzyl carbonates **180** and **181** were found to hydrolyse on standing to give the carbamates **178** and **179**.



Scheme 44: Synthesis of ethyl and benzyl pro-drugs

As with the previously synthesised analogues, the pro-drugs were tested in an MTS cell proliferation assay using human HT29 colon cancer cells with a 72 hr exposure time (Table 3). The activities of the compounds were found to be

comparable to that of the parent compound, showing that the addition of carbamate and carbonate groups to the compound did not have a deleterious effect on activity.

Table 3: Activities of parent compound 174 and its pro-drugs

Compound	**174**	**178**	**179**
Activity (μM)	71	83	95

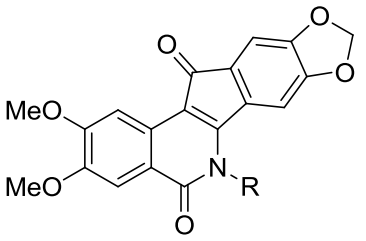
It was not known what the active species was within the assay, or at what point, if at all, the carbamate groups were hydrolysed. To evaluate this, the benzyl pro-drug **179** was incubated in the assay medium for 72 hrs, to mimic the assay conditions without the cells present. Aliquots of the media were taken at intervals an analysed by mass spectroscopy for the degradation of the pro-drug and appearance of the parent compound. The mass spectra showed the pro-drug to remain intact throughout the 72 hrs, without the appearance of the parent compound **174**. This shows that the pro-drug must be entering the cell, where it is either then hydrolysed to give the active compound or it stays intact and shows cytotoxicity itself.

2.5. CONCLUSIONS AND FUTURE WORK

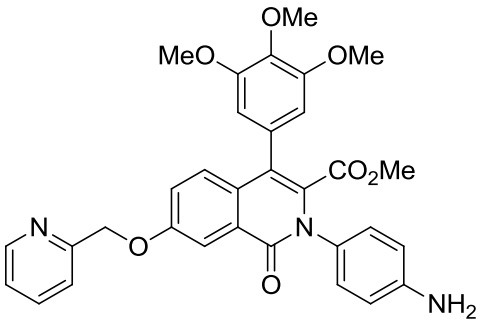
A one-pot method to synthesise a series of AB-ring analogues of narciclasine from their corresponding carboxylic acids has been developed and optimised, using a modified Curtius rearrangement and Lewis-acid catalysed intramolecular Friedel-Crafts alkylation. Using this procedure, twelve analogues have been synthesised in moderate to good yields. This procedure can now be applied in the synthesis of the more complex ABC-ring analogues.

The 6-membered ring analogues were all oxidised to give their fully aromatic counterparts which mimic the sp^2 position in narciclasine. Although DDQ was able to perform the oxidation of most of the analogues, the yields were generally poor and the procedure was not successful on all of the analogues. There was more success using palladium on carbon, especially when the reactions were performed in a microwave and in future this procedure should be used for the dehydrogenation of dihydroisoquinolinones and carbolinones.

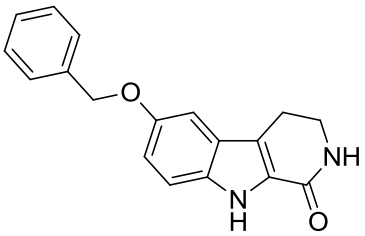
These analogues have been tested against HT29 colon cancer cells and were found to be poor to moderately cytotoxic. Despite these activities, these compounds are privileged structures which have been reported to be active against a range of targets when incorporated into larger molecules (Figure 32). The oxidised electron rich aromatic motif is found in the cytotoxic topoisomerase I inhibitor NSC 314622 **182** developed by Cushman.[125] 4-Aryl-1-isoquinolinone derivatives **183** have been found to inhibit phosphodiesterase 5, a target in the treatment of cardiovascular diseases.[126] Carbolinones, such as **184**, have also found to be glutamate receptor (mGluR) antagonists.[127] A series of carbolinones including **185** have been investigated as potent inhibitors of MK2, a kinase involved inflammation, cell proliferation and apoptosis.[121]



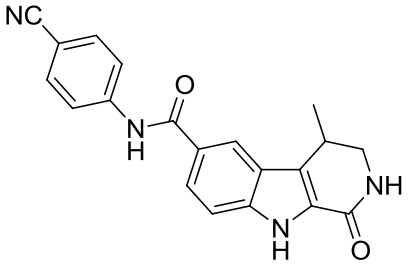
topoisomerase I inhibitor
NSC 314622
182



phosphodiesterase inhibitor
183



mGluR1 antagonist **184**

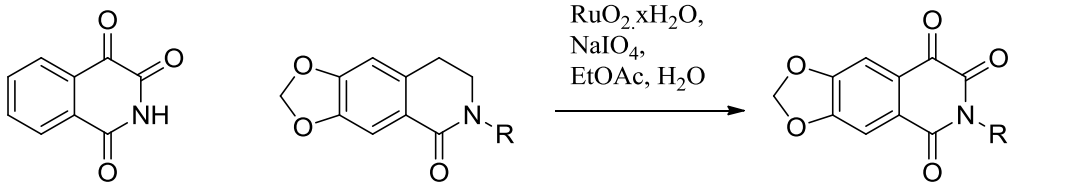


MK2 inhibitor **185**

Figure 32: Examples of AB-ring analogues incorporated into larger, bioactive molecules

To extend the work on the carbolinone series, preliminary experiments were performed into the Friedel-Crafts acylation of **153** at the 5-position using acetyl chloride and $AlCl_3$. Unfortunately, despite following literature precedent,[128] the compounds were not isolated during these initial investigations. However, further optimisation could provide a route to these medicinally interesting compounds.

In addition it has been found that triketone **186** is a caspase-3 inhibitor so is an inhibitor of apoptosis.[129] Ruthenium tetroxide, generated by the oxidation of ruthenium dioxide by sodium periodate, has been described for the oxidation of 3,4-dihydroisoquinolinones to the corresponding triketones.[130] In preliminary investigations, following this protocol, the oxidation of the methylenedioxy analogue **144** and its Boc-protected derivative **187** was investigated, however the corresponding triketones **188** and **189** were not observed.



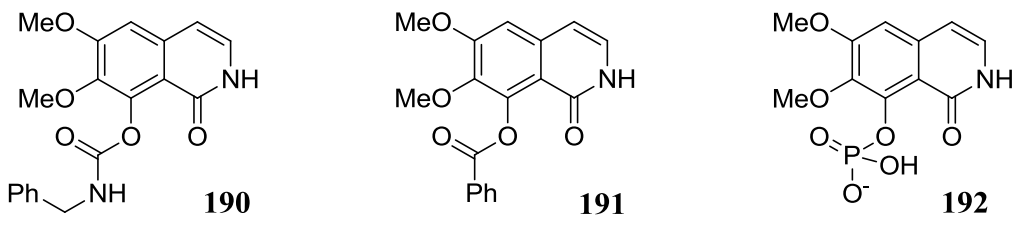
186

144: R = H
187: R = Boc

188: R = H, not observed
189: R = Boc, not observed

Scheme 45: Triketone 186 and the attempted oxidation of dihydroisoquinolinones

The benzyl and ethyl carbamate pro-drugs **178** and **179** have been prepared and evaluated using the HT29 colon carcinoma cell line and displayed only a small reduction in activity when compared to the parent compound. As the carbonate groups on the phenol in **180** and **181** were unstable under ambient conditions, other functional groups can be investigated to make use of this handle (Figure 33). Carbamates **190** can be synthesised using carbamoyl chlorides in the presence of strong base. Esters **191** can also be investigated as groups which are stable in ambient conditions, but susceptible to hydrolysis within the body. Within studies on narciclasine, the 1-phenyl ester was found to be active, however the 7-phenyl ester was not prepared. Phosphate esters **192**, similar to those of narciclasine discussed in section 1.1.4 (p. 14) can also be investigated.



190 **191** **192**

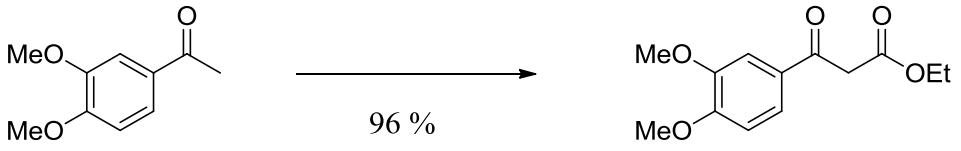
Figure 33: Examples of possible pro-drugs that could be investigated

3. SYNTHESIS AND EVALUTATION OF ABC-RING ANALOGUES

3.1. SYNTHESIS OF THE DIMETHOXY-ANALOGUE

3.1.1. Synthesis of the β-Ketoester

For the synthesis of the tricyclic core, the dimethoxy-substituted analogue was chosen as the model system as it simplifies the cyclisation of the B-ring in comparison to the trimethoxy-derivative which undergoes selective demethylation. The cost and availability of the starting acetophenone favoured the use of dimethoxyacetophenone over methylenedioxyacetophenone. The optimised synthetic route would then be applied to the synthesis of other analogues.



193 **194**

Reagents and conditions: 1.5 eq NaH, diethyl carbonate, 80 °C.

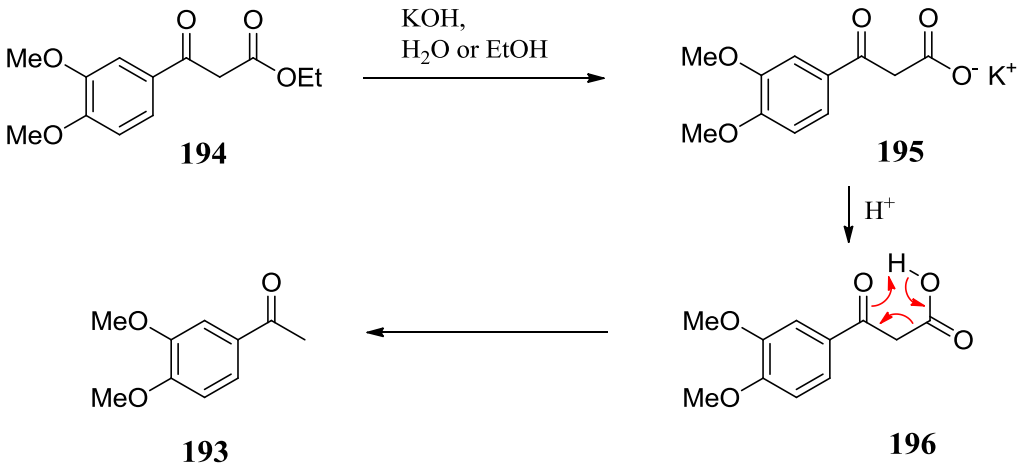
Scheme 46: Synthesis of β-ketoester 194

The first step in the synthesis was a Claisen condensation of 3,4-dimethoxyacetophenone **193** with diethyl carbonate (Scheme 46). Following the procedure reported by Jung *et al.*,[131] on a 10 mmol scale using sodium hydride as the base at 80 °C, the β-ketoester **194** was isolated in 97 % yield. The reaction has been repeated on a 50 mmol scale with a yield of 96 %, demonstrating the consistency and scalability in the reaction. Condensation of the β-ketoester with another molecule of the carbonate was not observed.

Following the proposed synthesis discussed in Section 1.2 (p. 20), there were two possible routes that could be taken from the β-ketoester to form the tricyclic core structure.

3.1.2. Route A

Following Route A, saponifaction of the β-ketoester was attempted, to provide the carboxylic acid for the Curtius rearrangement. Herbert *et al.* reported the saponification of ethyl ester **194** using aqueous KOH and isolated the resulting acid **196** in 82 % yield.[132] However, in our hands acid **196** could not be isolated, instead only ketone **193,** the product from decarboxylation was isolated (Scheme 47).



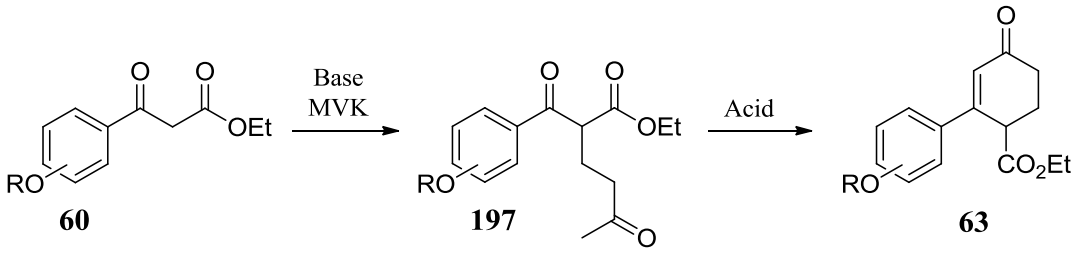
Scheme 47: Saponification and decarboxylation of β-ketoester

Treatment of β-ketoester **194** with KOH in EtOH gave the potassium carboxylate **195** in 84 % yield after filtration from the reaction mixture. As the free acid could not be isolated, the potassium carboxylate was subjected to the rearrangement and cyclisation conditions optimised with the AB-ring analogues (Section 1.2.1.), however the product was not isolated. As gas evolution had not been observed, it was believed that the isocyanate was not formed due to poor solubility of the potassium salt in toluene. In an attempt to solubilise the carboxylate **195**, 18-crown-6 was added to the reaction mixture to chelate to the potassium ion; however, the cyclised product was still not observed. Instead, the corresponding ethyl ester was isolated in 33 % yield, indicating that some of carboxylate had been activated, but residual ethanol from the saponification had acted as the nucleophile instead of the azide. The remainder of the mass could not be identified.

These experiments indicated that the cyclisation in route A would require further investigation and since the alternative route was more successful, further work on Route A was not performed.

3.1.3. Route B

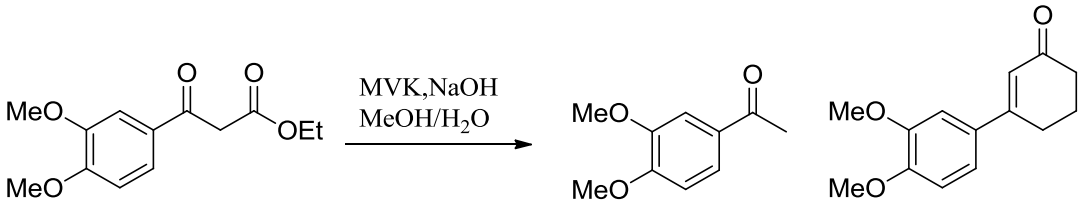
The first step in route B is the reaction of the β-ketoester **60** with methyl vinyl ketone (MVK) in a Robinson annulation to give a modified Hagemann's ester **63**. As previously discussed in the introduction; the mechanism proceeds via a Michael addition to the MVK, followed by an intramolecular aldol condensation to give the cyclohexenone (Scheme 48).



60 **197** **63**

Scheme 48: Simplified mechanism of the Robinson annulation

There are many examples of Robinson annulations in the literature, providing confidence in the approach. Using NaOH in MeOH, as reported by Ziegler,[133] Umbezawa[134] and Turnbull,[135] followed by acidification with sulfuric acid and heating to 70 °C gave a number of compounds, most of which could not be identified. However, two compounds were identified as the acetophenone **193** in 4 % yield and cyclised material **198** in 17 % yield (Scheme 49).

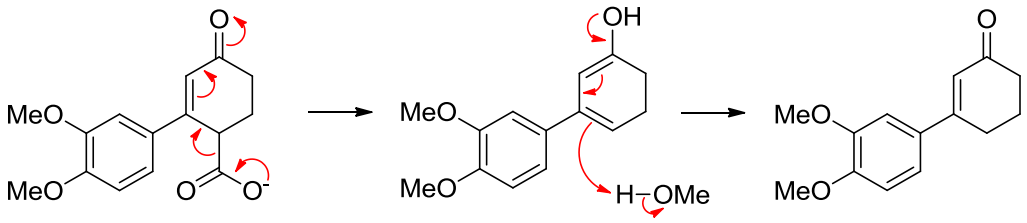


194 **193** 4 % **198** 17 %

Scheme 49: Reaction of β-ketoester 194 with NaOH as the base

The appearance of these compounds is due to hydrolysis of the ester group and subsequent decarboxylation. As previously described in Route A; the acidic work-up results in decarboxylation of the β-ketoacid **194** when hydrolysis occurs before the Robinson annulation resulting in acetophenone **193.** When hydrolysis

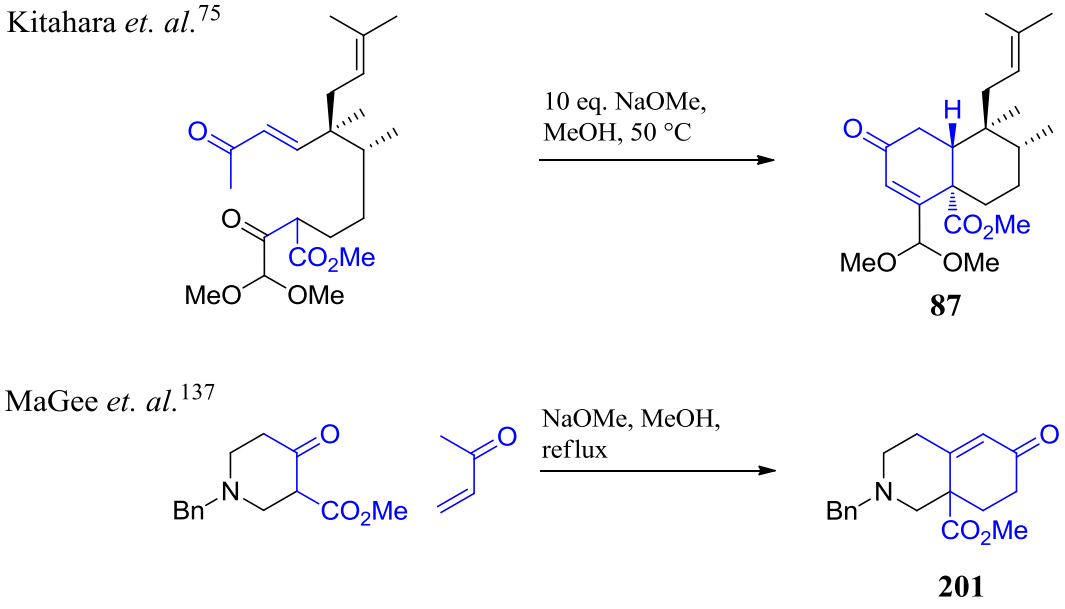
occurs in the cyclised material **199**, the extended conjugated system proves a route for decarboxylation under basic conditions as the ketone acts as an electron sink (Scheme 50). This observation has been reported Counsell *et al.* in their synthesis of androstenedione analogues.[136]



199 **200** **198**

Scheme 50: Mechanism of decarboxylation in cyclised material

As the cause of the saponification was due to the hydroxide, other bases were investigated. Sodium methoxide in methanol has been reported in similar systems by Kitahara in the synthesis of tanabalin **87**,[75] and MaGee in the synthesis of decahydroisoquinolines **201** (Scheme 51).[137]



Scheme 51: Kitahara's[75] and MaGee's[137] examples of NaOMe/MeOH mediated Robinson annulations

To prevent the formation of a mixture of the ethyl and methyl esters, sodium ethoxide in ethanol was used instead. Following a procedure reported by Aubé,[77] the β-ketoester **194** was treated with the MVK and NaOEt in EtOH, at 70 °C as reported and at room temperature. However, the main product from both reactions was the decarboxylated ketone **198**. Ethanol was used directly without distillation, so residual water could have led to de-esterification. The reactions were repeated with a preformed solution of NaOEt in EtOH under anhydrous conditions and after heating at both 50 °C and 90 °C, the main product isolated from the reaction was the β-ketoester **194**, with a small amount of the acetophenone **193**. This shows that in the absence of water de-esterification does not occur, but that NaOEt is still not a suitable base for the transformation. This may be because the enolate formed by the deprotonation of a β-ketoester can chelate a sodium ion, stabilising the negative charge and rendering it a poor nucleophile (Figure 34). A solution to this would be to use a base with a larger cation that is unable to coordinate so strongly to the enolate.

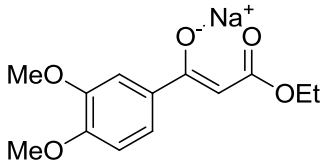
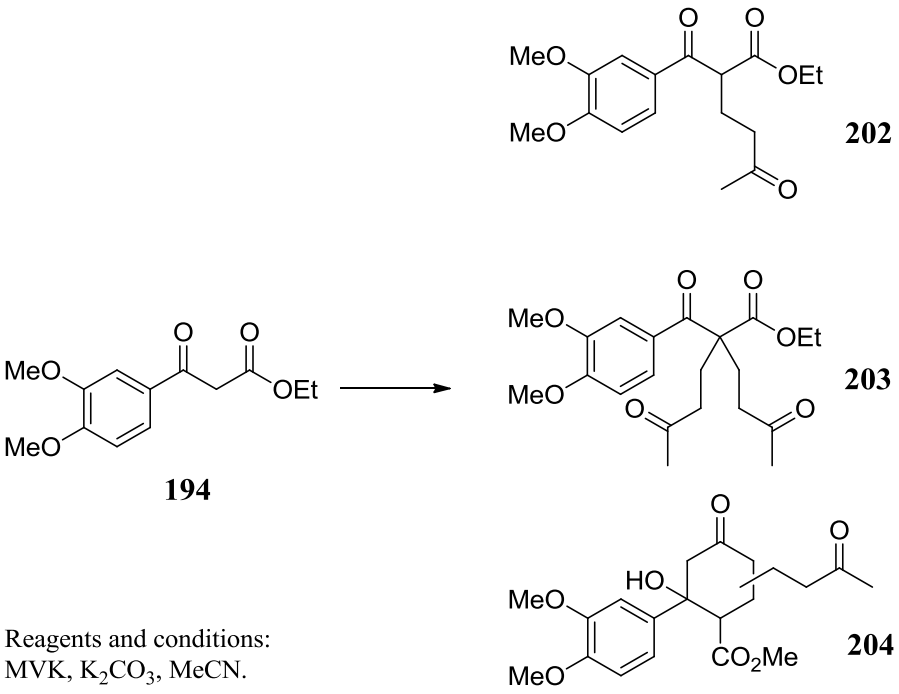


Figure 34: Chelation of sodium ion

Potassium carbonate was investigated as a non-nucleophilic base, with a larger counterion to avoid the problems of saponification and chelation. There is some literature precedent for the use of K_2CO_3, using alcohols as the solvent.[138] Alcohols are nucleophilic and generally hygroscopic, so to avoid the use of a nucleophilic solvent or the possible introduction of water, anhydrous acetonitrile was employed instead (Scheme 52).



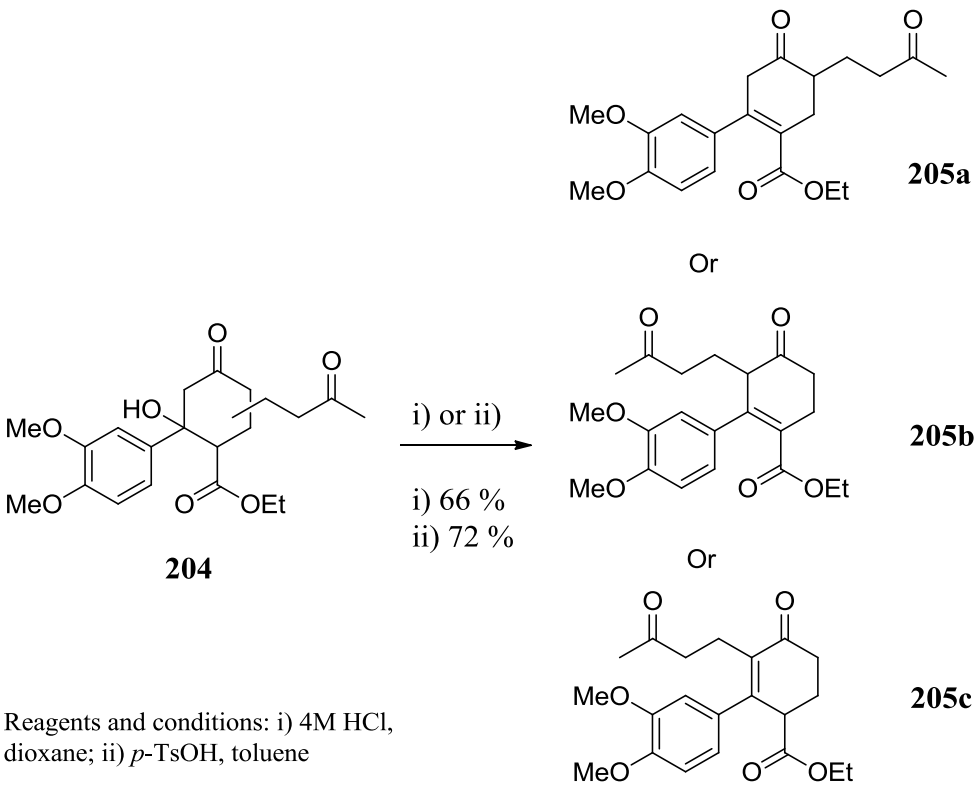
Scheme 52: Michael addition of ester to MVK in presence of K_2CO_3

Using 2.5 eq. of the base and MVK for 18 hrs at room temperature gave two products; the mono-addition product **202** in 72 % yield and the bis-addition product **203** in 9 % yield (Table 4, entry 1). Increasing temperature and reaction time were investigated to promote cyclisation to the modified Hagemann's ester **204** (Table 4, entries 2-4). However any cyclised material observed had also undergone a second Michael addition. As there are three sets of acidic protons in the cyclohexenone adjacent to a carbonyl group, there are three possible sites for this second addition to occur leading to three possible regioisomers, but the structure of the product could not be deduced by spectroscopic methods. Interestingly, the Michael addition product **202** can be formed in good yield under mild conditions (Entry 5).

Table 4: Optimisation of the reaction of β-ketoester 194 and MVK with K_2CO_3 in acetonitrile

Entry	K_2CO_3 (eq)	MVK (eq)	Time (hrs)	Temp (°C)	Yield 202 (%)	Yield 203 (%)	Yield 204 (%)
1	2.5	2.5	18	r.t.	72	9	-
2	2.5	2.5	24	50	11	18	56
3	1.5	1.5	24	50	34	5	28
4	1.5	1.5	5	80	Not recorded	Not recorded	40
5	1.1	1.1	2.5	0-rt	97	-	-

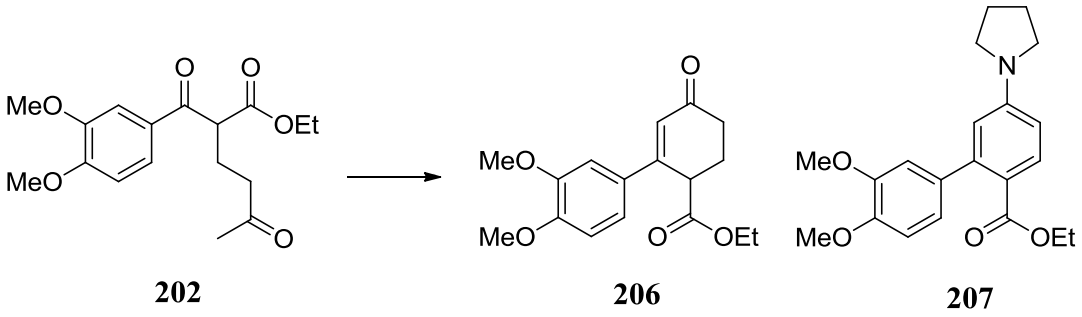
Dehydration of the cyclised material **204** under acidic conditions was performed to install the double bond (Scheme 53). Conditions similar to those reported by Jørgensen[96] utilising 4M HCl in dioxane yielded 66 % of the dehydrated product **205** and 20 % starting material. When *p*-TsOH in refluxing toluene was employed, as described by Agami,[93] only the dehydrated product **205** was isolated in a 72 % yield. The site of the second Michael addition could still not be deduced by spectroscopic methods, but the absence of an alkenyl proton in the ^{1}H NMR spectrum implied that the second Michael addition did not occur adjacent to the ester group.



Scheme 53: Dehydration of alcohol 204 to give one of three possible regioisomers 205a, b or c

Due to the success of the mild Michael addition reaction conditions it was decided to approach the annulation as a two step process. There was literature precedent for performing the cyclisation and dehydration in one step from the Michael addition product **202** in acidic conditions including the use of pyrrolidine or piperidine and acetic acid as described by Golding[86] and Christoffers.[82] Following the conditions reported by Boeckman,[80] ester **202** was heated in toluene in refluxing

conditions with 3 eq. pyrrolidine and 4 eq. of acetic acid for 24 hrs, giving the desired cyclised product **206** in only 16 % yield (Table 5, entry 1). In addition aniline **207** was also isolated in a 25 % yield, presumably generated by the condensation with pyrrolidine and subsequent oxidation to give the aromatic ring (Scheme 54).



202 **206** **207**

Reagents and conditions: Pyrrolidine, AcOH, toluene

Scheme 54: Cyclisation of Michael addition product 202 using pyrrolidine and acetic acid

Formation of similar aniline products has been described by Padwa where a cyclisation of a Michael addition product was carried out in the presence of an excess of pyrrolidine and catalytic *p*-TsOH acid in refluxing toluene.[139] To avoid the formation of the aniline, different conditions were investigated (Table 5).

Table 5: Optimisation of pyrrolidinium acetate promoted cyclisation

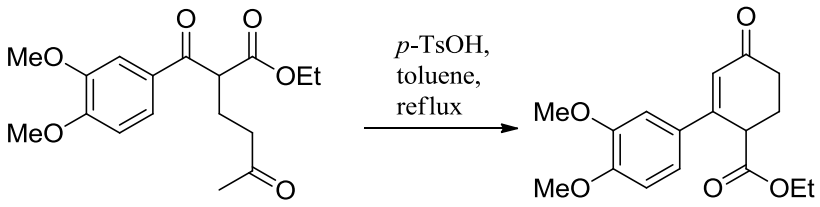
Entry	Pyrrolidine (eq)	AcOH (eq)	Time (hrs)	Temp (°C)	Yield 206 (%)	Yield 207 (%)
1	3	4	24	Reflux	16	25
2	0.8	0.95	1.5	80	65[a]	-
3	0.8	0.95	2.5	80	52	-

[a] isolated as a mixture of starting material **202** and product **206** in a 15:85 ratio.

Following the conditions reported by Nour, the reaction was performed using a substoichiometric amount of pyrrolidine and AcOH at 80 °C and the aniline was not observed (Table 5, entries 2 and 3). However, full conversion of the starting material to product was not achieved when the reaction was stirred for only 1.5 hrs (Entry 2). Full conversion of the starting material to the product was essential as the

compounds could not be separated by column chromatography and this was achieved in 2.5 hrs (Entry 3).

As lowering the temperature from reflux to 80 °C resulted in an increase in yield, further increases in yield may be achieved by reducing the temperature further but increasing the reaction time. This method holds promise in also providing an enantioselective route to the cyclohexenone by using chiral secondary amines or proline derivatives; an approach which has been used by Jørgensen *et al.* in the enantiomeric synthesis of cyclohexenones.[96]



202 **206**

Scheme 55: *p*-TsOH catalysed cyclisation of 202

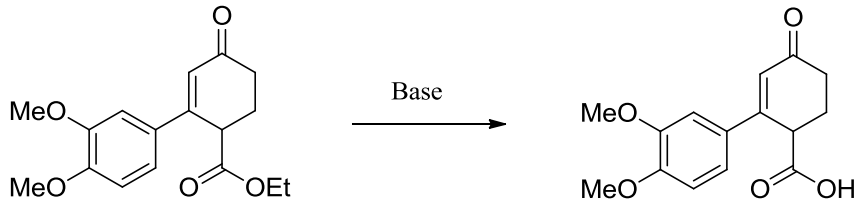
Liu[84] and Agami[93] have reported the use of *p*-TsOH in toluene to affect the cyclisation and dehydration (Scheme 55). Initially 10 mol% of the *p*-TsOH catalyst was employed; however there was only a 30 % conversion of the starting material to product after 24 hrs (Table 6, entry 1). As previously highlighted, full conversion was essential for a successful reaction as the starting material and product could not be separated by column chromatography. When the amount of the catalyst was increased to 30 mol%, there was an increase in conversion to 66 % (Entry 2) and full conversion was only achieved using 40 mol% of the catalyst (Entry 3). Increasing the amount of catalyst to 60 mol% did not increase the yield further (Entry 4).

When the reaction was performed on a larger scale, a basic work-up was included to remove the increased quantity of *p*-TsOH; however an increase in yield was not observed so this was excluded from subsequent reactions (Entry 6).

Table 6: Optimisation of the acid catalysed cyclisation

Entry	Scale (mmol)	*p*-TsOH (mol%)	Time (hrs)	% Product 202	% Starting material 207
1	0.5	10	24	30	70
2	0.5	30	24	66	34
3	0.5	40	20	89	-
4	0.5	60	24	74	-
5	3	40	38	70	-
6	9.3	40	20	70	-

With a route to the modified Hagemann's ester **207** in hand, investigations began on the saponification of the ester and the rearrangement and cyclisation of the resulting acid. There had already been indications the acid may be difficult to handle due to the extended conjugated system allowing decarboxylation. However, it was thought that if the acid could be kept cool until the acyl azide intermediate had been formed then decomposition could be avoided.



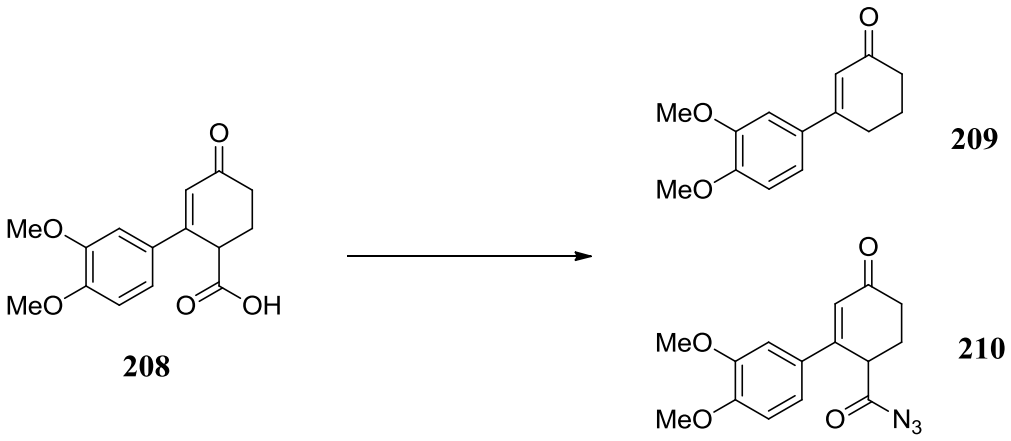
206 **208**

Scheme 56: Saponification of ester 206

There was some literature precedent for the saponification reaction, all of which kept the reactions cool to avoid decarboxylation. Using $LiOH.H_2O$ in $MeOH/H_2O$ at 10 °C for 5 hrs as described by Bannerjee,[140,141] or NaOH in $MeOH/H_2O$ at 5 °C for 24 hrs as described by Rosenberger,[142] both gave mixtures of products which could not be separated. The most successful conditions found were those reported by Oritani,[143] using 1.1 eq. of KOH in $EtOH/H_2O$ at 5 °C overnight. This reaction was performed several times during the investigation with yields of acid **208** of 80 % to quantitative. Practically, the reaction was easy to execute as it could be left in the fridge overnight. It was found that extractions needed to be

performed with diethyl ether as the organic phase because hydrolysis of ethyl acetate was observed leading to trace amounts of acetic acid contaminating the product.

Cyclisation of the acid **208** was attempted using the procedure optimised on the AB-ring analogues, but to activate the acid and form the acyl azide without concurrent decarboxylation, the reaction was cooled to 5 °C for 1 hr before heating to 90 °C. Two products were isolated from the reaction in a 1:1 ratio, but could they not be separated by column chromatography; the decarboxylated material **209** and what was thought to be the acyl azide **210** as determined by a characteristic peak in the IR at 2145 cm^{-1} correlating to an azide stretching frequency (Scheme 57).



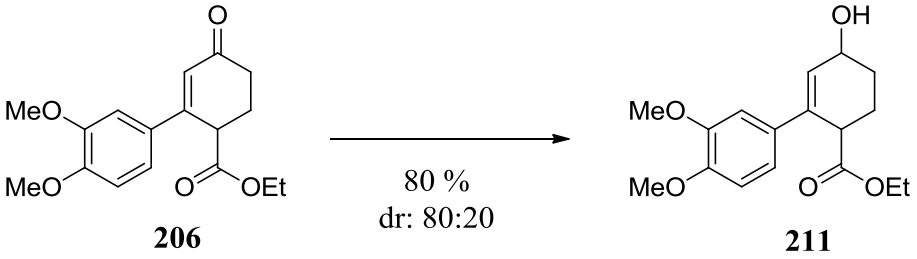
Reagents and conditions: a) DPPA, Et_3N, toluene, 5 °C; b) 90 °C; c) $BF_3 \cdot OEt_2$

Scheme 57: Attempted cyclisation of acid 208

To prevent the problem of decarboxylation, it was decided that the extended conjugated system should be removed before the further cyclisation conditions were attempted. This was achieved by reduction of the ketone, followed by protection of the resulting alcohol to prevent interference with the cyclisation reaction.

The Luche reduction uses sodium borohydride and ceric chloride to selectively reduce an α,β-unsaturated ketone whilst leaving the alkene intact.[144] Following the method of Hudlicky *et al.*,[145] the ketone **206** was successfully reduced to afford alcohol **211** in 80 % yield and an 80:20 mixture of diastereoisomers (Scheme 58). It was not possible to identify which was the major isomer by spectroscopic methods. However, mechanistically the hydride would be

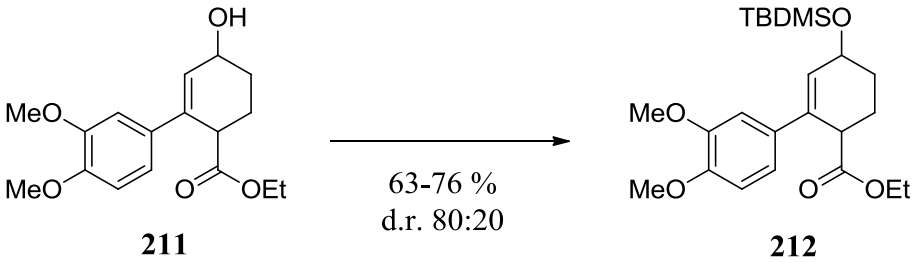
preferentially delivered to the least hindered face of the carbonyl. This would place the hydroxyl and ester groups on the same face of the ring in the major isomer.



Reagents and conditions: $NaBH_4$, $CeCl_3$, MeOH

Scheme 58: Luche reduction of unsaturated ketone 206

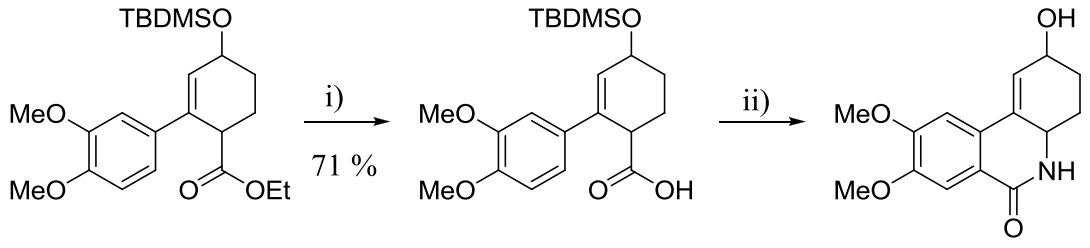
Protection of an alcohol using a silyl group is a common protection strategy,[146] as the protection is straightforward to perform under basic conditions and the deprotection can be affected by either fluoride or under acidic conditions. It was also anticipated that using $BF_3 \cdot OEt_2$ as the Lewis acid in the cyclisation would provide a source of F^-, negating the need for a formal deprotection at the end of the synthesis. *tert*-Butyldimethylsilyl (TBDMS) chloride was chosen to protect the alcohol, as the TBDMS group would be more stable to the acidic work-up involved in the saponification step. The conditions chosen were those reported by both Shimizu,[147] and Petit,[148] using 1.1 eq. TBDMSCl and 1.1 eq. imidazole in DMF and produced the protected alcohol **212** in 63 % yield when performed on a 0.4 mmol scale and a 76 % yield when the scale was increased to 3 mmol (Scheme 59). The product remained an 80:20 mixture of diastereoisomers, but again the configuration of the major isomer could not be determined by ^{1}H NMR analysis.



Reagents and conditions: TBDMSCl, imidazole, DMF.

Scheme 59: Silyl protection of the alcohol 211

The ester **212** was exposed to the same saponification conditions previously used, however it was discovered that this ester was more stable to these conditions and so heating was required to force the reaction (Scheme 60). The acid was isolated in approximately 71 % yield, but the product contained minor impurities by ^{1}H NMR analysis. Cyclisation was attempted on the material using DPPA and Et_3N in toluene at 90 °C followed by treatment with $BF_3{\cdot}OEt_2$. However, a mixture of products was isolated which could not be identified by spectroscopic methods.



212 **213** **214** not observed

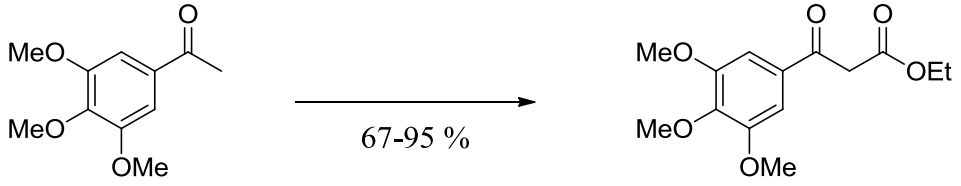
Reagents and conditions: i) KOH, EtOH/H_2O, reflux; ii) a) DPPA, Et_3N, toluene, 90 ºC; b) $BF_3{\cdot}OEt_2$

Scheme 60: Saponification and attempted cyclisation of ester 212

3.2. SYNTHESIS OF THE TRIMETHOXY-ANALOGUE

3.2.1. Synthesis of the Modified Hagemann's Ester

The initial steps in the synthesis were straightforward as the route previously developed from 3,4-dimethoxyacetophenone could be used. The Claisen condensation using NaH in diethyl carbonate was successful and the reaction was performed 3 times on scales of 5-50 mmol, with yields of 67-95 % (Scheme 61).

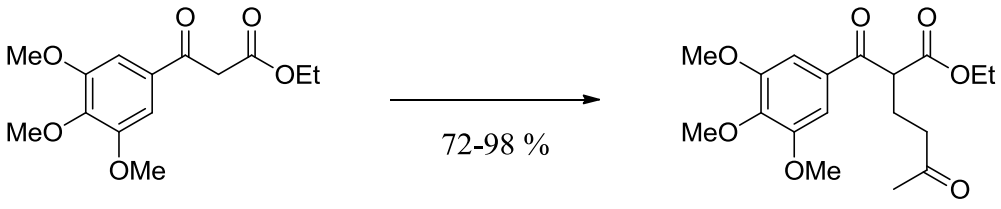


215 **216**

Reagents and Conditions: NaH, diethyl carbonate, 80 °C, 1-3 hrs.

Scheme 61: Condensation of acetophenone with diethyl carbonate

The Michael addition using 1.1 eq. MVK and 1.1 eq. K_2CO_3 in MeCN was also efficient, with yields of the Michael adduct **217** of 72-98 % over the 3 times the reaction was performed (Scheme 62). Both steps have been performed on scales of up to 50 mmol, showing the robustness of the reactions. Column chromatography was used to purify the products; however there is opportunity to telescope the products through to the solid Hagemann's ester **218**, which can be purified by recrystallisation, avoiding the use of chromatography on a large scale.

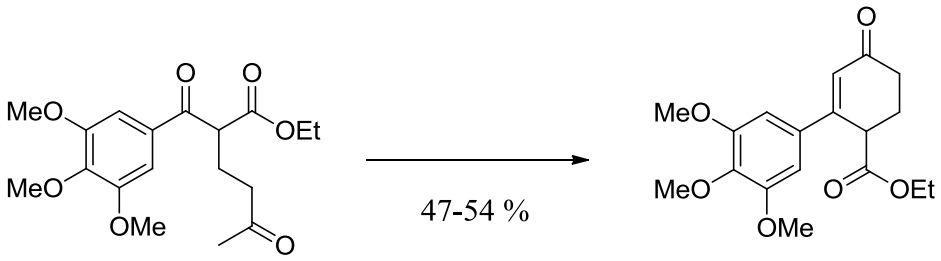


216 **217**

Reagents and conditions: MVK, K_2CO_3, MeCN, 0 ºC-r.t.

Scheme 62: Preparation of 217 by the Michael addition of MVK to β-ketoester 216

The conditions used for the cyclisation were those previously developed on the dimethoxy-analogue using 0.4 eq. of *p*-TsOH in refluxing toluene (Scheme 63). The reaction was performed on 26-40 mmol scale using Dean-Stark trap to afford the ester **218** in 47-54 % yield.



217 **218**

Reagents and conditions: 0.4 eq *p*-TsOH, toluene, reflux, 24 hrs.

Scheme 63: Acid catalysed cyclisation of 217

The remainder of the mass balance was not determined. However, as ^1H NMR analysis of the crude reaction mixture showed clean conversion of the starting material to product, the poor yield was believed to be due to problems during

purification. In future, column chromatography might be avoided and yields increased by employing a basic work-up and recrystallisation to purify the product.

3.2.2. Saponification and Cyclisation of Modified Hagemann's Ester

The optimised conditions for the hydrolysis of the dimethoxy- analogue **206** using 1.1 eq. KOH in EtOH/H_2O were unsuccessful, giving a mixture of products that could not be separated. A screen of bases and solvents was undertaken, leaving the reactions at 5 °C for 16 hrs, with the best results obtained with 5 eq. of LiOH.H_2O in EtOH/H_2O (Table 7, entry 1). The ^{1}H NMR spectra of the crude acid **219** were cleaner when the reaction was performed in EtOH/H_2O than when THF/H_2O was used. After the initial screen it was found that the reactions could be performed at room temperature, giving yields of 75-97 % in just 1 hr.

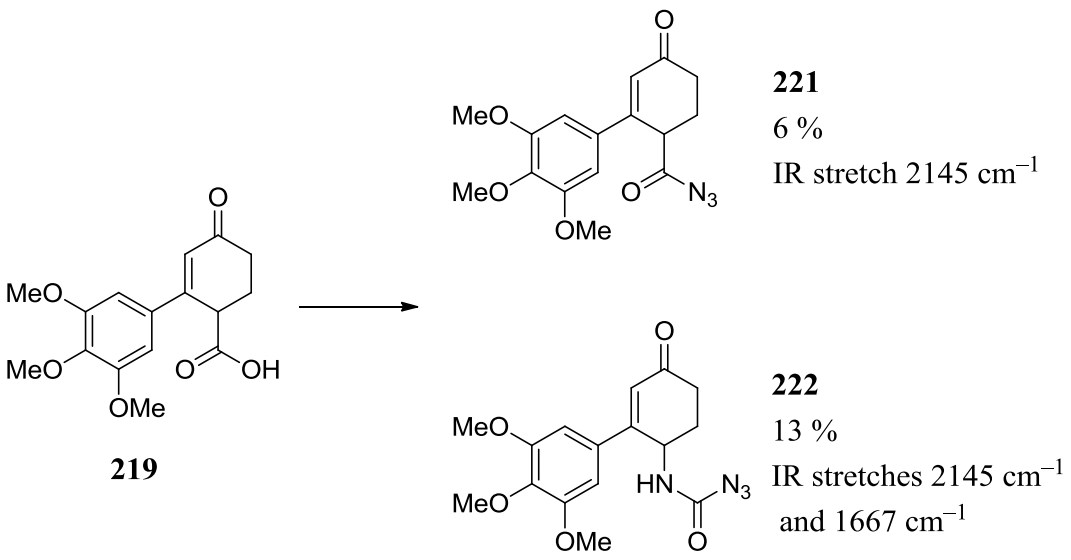
Table 7: Screen for conditions for the saponification of ester 218

Entry	Base	Solvent	Result
1	LiOH.H_2O	EtOH/H_2O	Clean, complete conversion by ^{1}H NMR and TLC
2		THF/H_2O	Complete conversion by TLC but impurities present by ^{1}H NMR
3	NaOH	EtOH/H_2O	Clean, complete conversion by ^{1}H NMR and TLC
4		THF/H_2O	Incomplete conversion.

For the first attempt at the Curtius rearrangement, the acid was stirred at room temperature with triethylamine and DPPA in toluene for 45 mins before the reaction has heated at 90 °C. As was observed during the rearrangement of the dimethoxy- analogue under similar conditions (Section 3.1.3, p. 69), the reaction yielded a mixture of products which could not be separated by column chromatography. However the decarboxylated product **220** could be identified in the ^{1}H NMR spectrum of the crude material. It was believed that the acid was not converted to the acyl azide before the reaction was heated, allowing decarboxylation to occur when the temperature was raised.

The isolation of acyl azides has been reported by Padwa[149] and Katrizky,[150] so to further investigate the activation of the acid isolation of the acyl azide **221** was

attempted. When reaction of acid **219** with DPPA and Et_3N was performed at room temperature, the acyl azide **221** was isolated in a disappointing 6 % yield, along with another product which appeared to be a carbamoyl azide **222** (Scheme 64). The IR spectrum of the compound **222** showed both amide and azide stretches at 1667 cm^{-1} and 2145 cm^{-1} respectively and the ^1H NMR spectrum of the compound contained 2 aromatic protons, indicating that cyclisation had not taken place. Carbamoyl azides have been reported, along with their synthesis from isocyanates and a source of azide.[151,152,153] Interestingly, to form this product the azide must undergo a room temperature Curtius rearrangement.

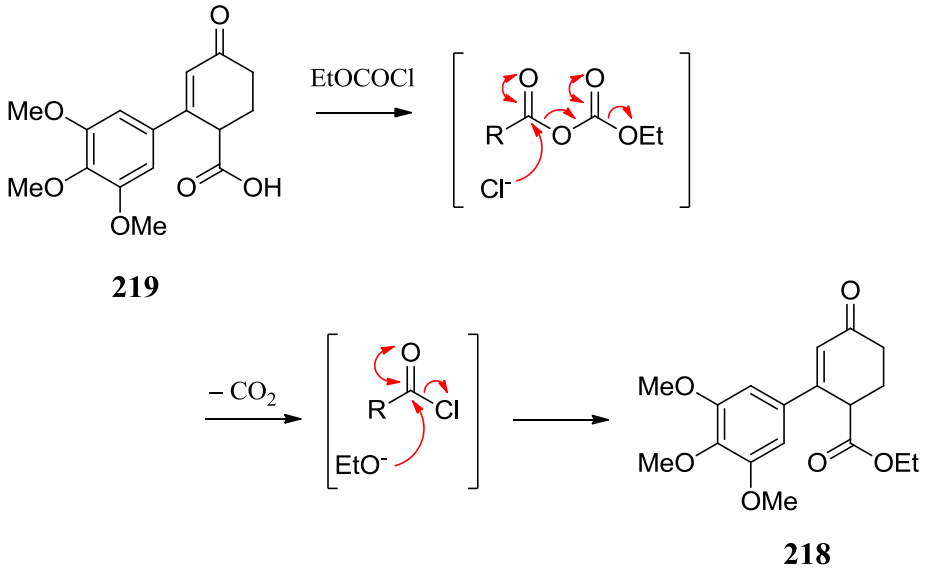


Reagents and conditions: DPPA, Et_3N, toluene, r.t., 2 hrs

Scheme 64: Attempted synthesis of the acyl azide

Activation of the acid using a mixed anhydride, as previously discussed in the synthesis of the AB-ring analogues, was also investigated. The reaction was performed at room temperature using ethyl chloroformate and Et_3N in acetone/water followed by the addition of NaN_3 to generate the acyl azide, however the acyl azide was not observed. Instead, the starting acid **219** was isolated in 45 % yield and the corresponding ethyl ester **218** was isolated in 47 % yield. The initial step in the mechanism of the formation of the ester is the activation of the acid as the mixed anhydride, with the liberation of a chloride anion. This can react as a nucleophile with the ester carbonyl, to give the acyl chloride with concurrent decomposition of

the carbonate moiety releasing carbon dioxide and ethoxide. Finally, the ethoxide displaces the chloride to give the ester **218** (Scheme 65).



Reagents and conditions: a) EtOCOCl, Et_3N, acetone/H_2O, r.t; b) NaN_3, acetone/H_2O

Scheme 65: Mechanism for the formation of ethyl ester 223 from acid 219 and EtOCOCl

As the acid **219** had been sensitive to the base used during the saponification step, other bases were considered for this transformation. Pyridine was identified as an alternative organic base. With a pK_a of 5.21, it is weaker than Et_3N with a pK_a of 10.75 but still basic enough to deprotonate the acid. Using DPPA to activate the acid, only the decarboxylated material **220** was observed (Scheme 66).

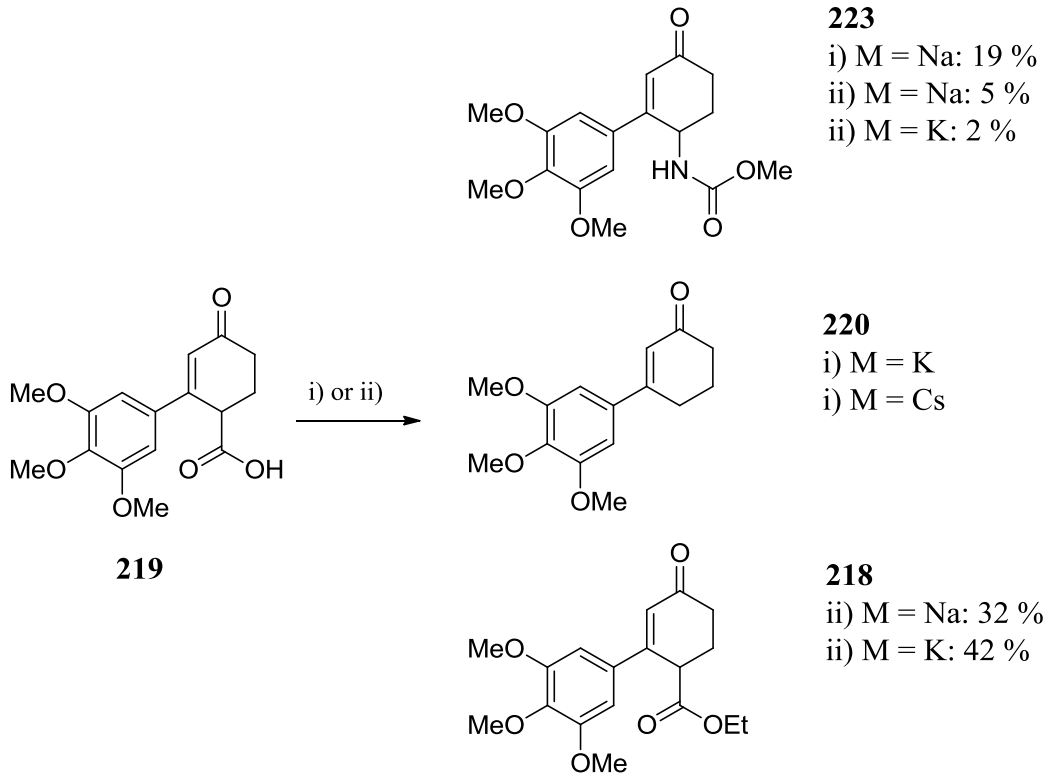
Reagents and conditions: a) DPPA, pyridine, toluene, r.t. 2 hrs; b) 90 °C, 1 hr; c) $BF_3{\cdot}OEt_2$.

Scheme 66: Using pyridine as the base in the Curtius rearrangement

Inorganic bases were also investigated as the saponification of ester **218** was successful when $LiOH.H_2O$ and NaOH were used, so these bases were known to be compatible with the carboxylate. However, hydroxide is nucleophilic so to avoid degradation of the DPPA or the activated acid, sodium, potassium and caesium carbonates were investigated instead. To improve the solubility of the base, the solvent was changed to acetone. In addition, the final step was also modified; after stirring the acid, carbonate and DPPA in acetone at room temperature, the solvent was removed and methanol added. This modification was an attempt to simplify the final step of the reaction, using the methanol to trap the isocyanate to give the carbamate instead of performing the cyclisation and demethylation (Scheme 67).

The carbamate **223** was isolated in 19 % yield when Na_2CO_3 was employed as the base. Carbamate **223** was also observed in the reaction using K_2CO_3 although the major product was that of decarboxylation **220**. The reaction with Cs_2CO_3 also gave predominantly decarboxylated material. These results were unsurprising as in the initial saponification reactions using KOH had given a mixture of products. It was believed that the carboxylate was unstable when accompanied by larger counterions.

Sodium and potassium carbonate were also employed as bases when ethyl chloroformate was used to activate the acid. It was believed these reactions would work well as the base would be fully dissolved in the acetone/water solvent system normally used. However; the predominant product in both reactions was the corresponding ethyl ester **218** that had previously been observed, isolated in 32 % yield using sodium carbonate and 42 % using potassium carbonate. The carbamate **223** was isolated in both reactions in a 5 % yield with Na_2CO_3 and 2 % with K_2CO_3.

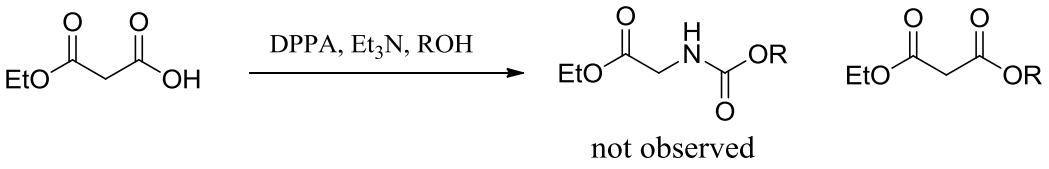


Reagents and conditions: i) a) M_2CO_3, DPPA, acetone, r.t., 1 hr; b) reflux 1 hr; c) MeOH, r.t.; or ii) a) M_2CO_3, EtOCOCl, acetone/H_2O, r.t.; b) NaN_3, H_2O; c) MeOH, reflux.

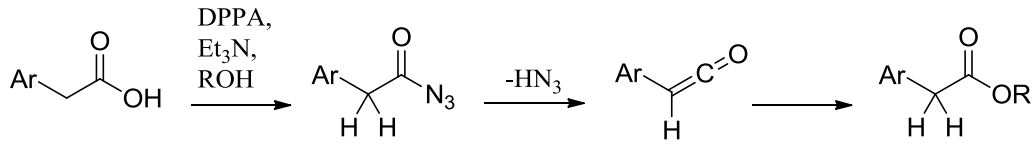
Scheme 67: Attempted cyclisation using carbonates as the base

Activating the acid as either a mixed anhydride or phosphoric anhydride was proving to be a difficult strategy, so the acid chloride was explored as a possible route of activation. In the attempted synthesis of α-amino acids from malonic half esters, it was found that using DPPA led to the formation of esters as the major product (Scheme 68).[154] It has been discussed more recently by Peterson *et al.* that this observation is due to the presence of acid protons alpha to the carboxylic acid leading to the formation of a ketene by the release of hydrazoic acid,[155] and they extended this idea to the presence of benzylic protons α- to the carboxylic acid. To avoid this, the acid can be activated as an acid chloride using oxalyl chloride and catalytic DMF.

Yamada *et. al.*[154]:



Peterson *et. al.*[155]:



Scheme 68: Formation of esters using DPPA via the loss of HN_3

Following the procedure reported by Peterson *et al.*,[155] the acid chloride formation was carried out at 0 °C for 1 hr, then the NaN_3 was added and finally the reaction mixture was treated with $BF_3{\cdot}OEt_2$. Neither the lactam nor the decarboxylated products were observed in the reaction, instead fluorenones **224** and **225** were isolated in a 9 % and 28 % yields (Scheme 69).

Reagents and conditions: a) $(COCl)_2$, DMF, CH_2Cl_2; b) NaN_3, acetone/H_2O; c) $BF_3{\cdot}OEt_2$.

Scheme 69: Formation of fluorenones 224 and 225 via the acid chloride

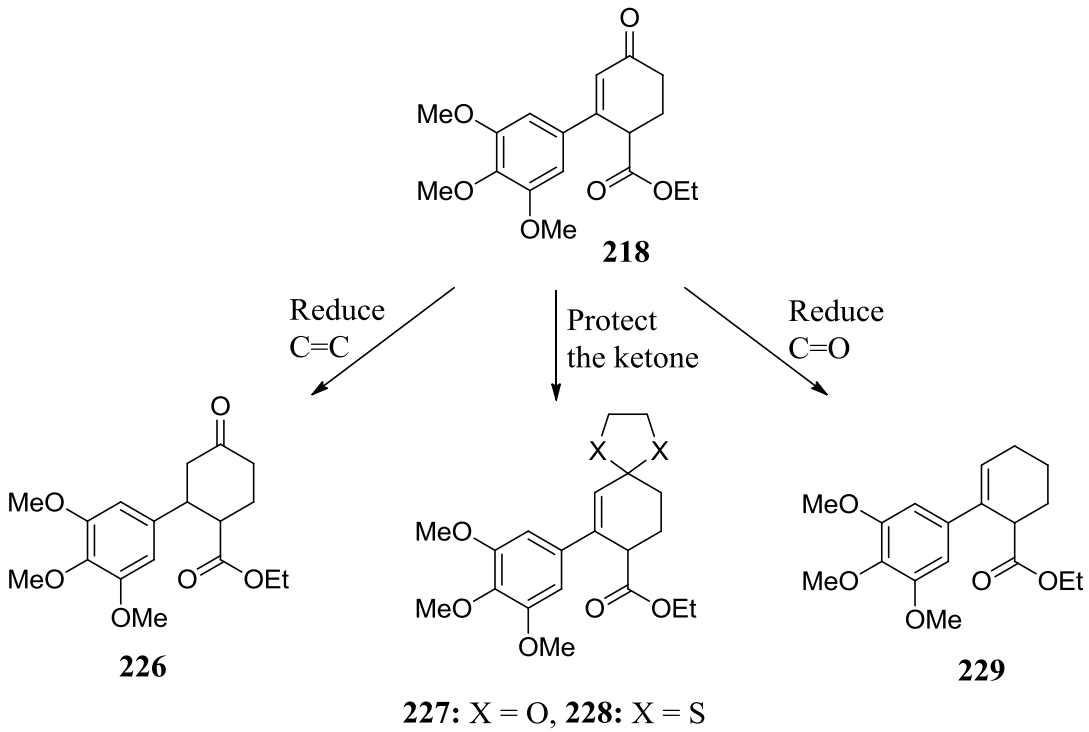
This shows that the acid can be activated as an acid chloride however the intramolecular nucleophilic attack of the electron-rich trimethoxyaryl group is much faster than the intermolecular attack of the sodium azide. Reducing the temperature of the reaction was explored as a way of reducing the rate of the intramolecular

reaction and increasing the chance of the intermolecular reaction. Targeting the acyl azide to ensure the intermolecular reaction had taken place, the acid chloride formation was carried out at −13 °C for 5 mins before the addition of sodium azide, but the 72 % of the starting material was reclaimed. When the reaction was left for 15 mins at −13 °C before the addition of azide only 65 % of the starting material was reclaimed. In these two reactions some decarboxylated cyclohexenone **220** was also observed, but the fluorenones were not seen. The acid chloride formation was also carried out at −10 °C for 1 hr before the addition of sodium azide and using methanol in the final step to target the carbamate **223**. The decarboxylated material **220** was isolated in 23 % yield and the fluorenone **225** isolated in 57 % yield but the carbamate was not observed. This final reaction shows that the intramolecular cyclisation of the acyl chloride is too fast in comparison to the formation of the acyl azide, so this method of activation was not suitable for this synthesis.

It was concluded that the difficulties in activating the acid **219** towards nucleophilic attack of azide, without concurrent decarboxylation or cyclisation, were due to the extended conjugated system with unsaturated ketone. It was believed that removing this system would allow the rearrangement to work, without the complications experienced so far.

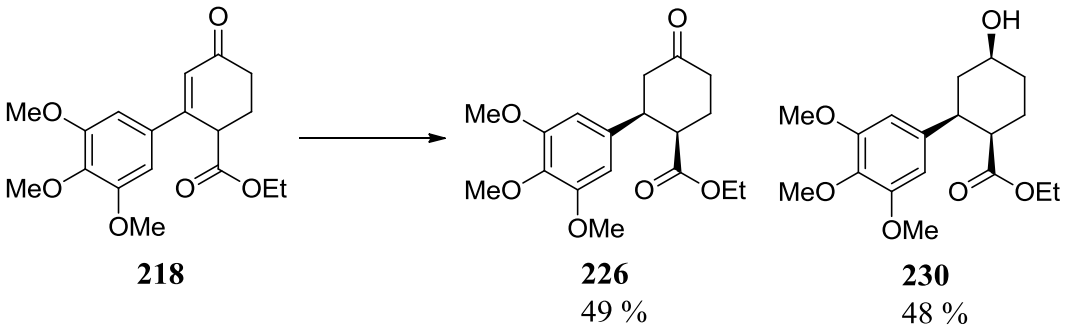
3.2.3. Removing the Conjugated System to Aid Cyclisation

Several methods of removing conjugation connecting the ester and ketone have been considered (Scheme 70). Luche reduction and silyl protection of the resulting alcohol had already been examined, but provided difficulties in saponification and cyclisation. Considering these problems, it seemed unwise to follow this route at this point. The other avenues investigated were to remove the cyclohexenyl double bond by hydrogenation leaving the ketone intact; protecting the ketone as either an acetal or dithioacetal; or completely removing the allyl ketone by reduction



Scheme 70: Considered methods of removing the conjugated system in ketone 218

The first method investigated was the hydrogenation of the double bond, leaving the ketone in place. Reduction of an α,β-unsaturated carbonyl with hydrogen and palladium on carbon is a well known transformation described extensively in the literature including examples by Cieplak,[156] Mateos in the synthesis of ohchinolide analogues[157] and Li in the synthesis of Cephalotaxine.[158] Using 5 mol% Pd/C in EtOAc, the double bond was reduced to furnish **226** in a 49 % yield, but concurrent over-reduction also gave alcohol **230** in a 48 % yield (Scheme 71).



Reagents and conditions: H_2, 5 mol% Pd/C, EtOAc.

Scheme 71: Hydrogenation of the α,β-unsaturated ketone

The desired product **226** was isolated as a single diastereoisomer, believed to be the *cis*-diastereomer by ^{1}H NMR analysis and mechanistic insights. As shown in Figure 35, generated using an MM2 calculation in Chem3D, the ester group sits directly over one face of the cyclohexyl ring, preventing the catalyst accessing this face, resulting in the hydrogen being delivered to the opposite face, pushing the aromatic ring onto the same face as the ester.

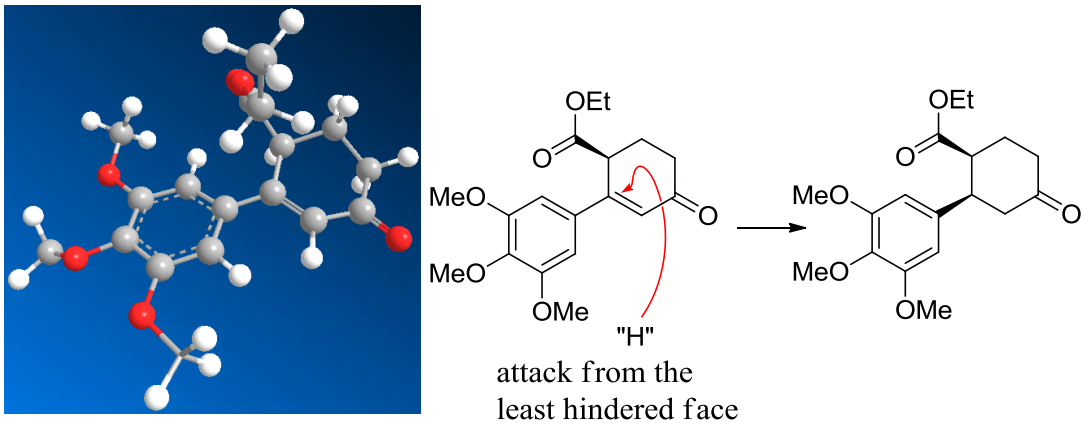
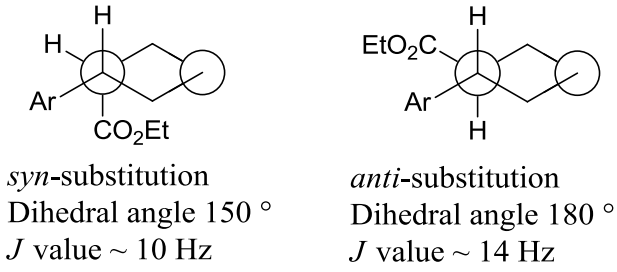


Figure 35: Origins of stereoselectivity in the hydrogenation

The protons at the C1 and C2 position of the cyclohexene ring have a coupling constant of 10.0 Hz in the ^{1}H NMR spectrum, so using the Karplus curve the protons and therefore the substituents have a *syn*-relationship (Figure 36).



syn-substitution
Dihedral angle 150 °
J value ~ 10 Hz

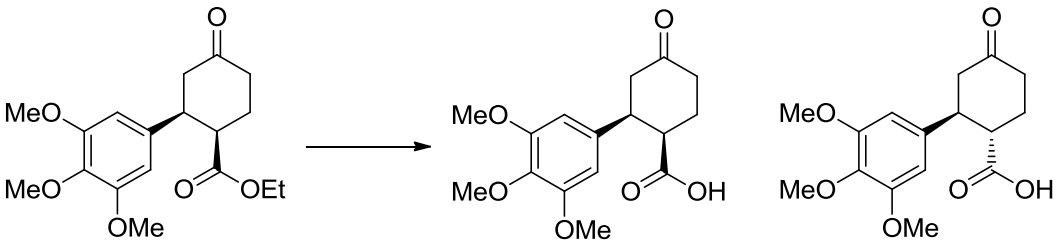
anti-substitution
Dihedral angle 180 °
J value ~ 14 Hz

Measured *J* value = 10.0 Hz ∴ the ester and aromatic ring are *syn*

Figure 36: Coupling constants of protons on the cyclohexyl ring

Over-reduction using Pd/C has been reported by Ohashi,[159] and Doering, [160] although they describe longer reaction times and higher pressures than were applied in this reaction. The alcohol **230** appears to be a single diastereoisomer by ^{1}H NMR

analysis, though the stereochemistry cannot by confirmed by the coupling constants. However, using the same mechanistic arguments as applied to the ketone **226**, a *syn*-relationship should exist between the alcohol, aryl ring and ester. The effect of changing the solvent to ethanol or acetic acid on the selectivity of the reaction was investigated, however over-reduction was always observed.



226 ***syn*-231** ***anti*-231**

Reagents and conditions: $LiOH.H_2O$ or NaOH, H_2O.

Scheme 72: Epimerisation and saponification of ester 226

Saponification of ester **226** was investigated using $LiOH.H_2O$ and NaOH and higher yields of acid **231** were achieved with shorter reaction times using NaOH (Table 8, entries 2 and 3).

Table 8: Epimerisation and hydrolysis of ester 226

Entry	Base	Reaction time (hrs)	Reaction temperature (°C)	Yield (%)	Diastereomeric ratio
1	$LiOH.H_2O$	5	r.t.	32	59:41
2	NaOH	1.5	Reflux	99	35:65
3	NaOH	3	Reflux	82	33:67

The natural product has an *anti*-relationship at the B/C ring junction, so it was envisioned that this geometry could be installed in acid **231** by concurrent base-catalysed epimerisation at the C1 position (Scheme 72). Some epimerisation was observed with the best conversions seen in the reactions using NaOH (entries 2 and 3); however, full conversion was not achieved in the timeframes investigated. This may be because mechanistically the epimerisation must occur before the saponification as otherwise the base needs to deprotonate an anionic species which is energetically unfavourable. This means if the saponification reaction is faster than epimerisation, full conversion of the stereocentre would be slow. If this route was to

be pursued further then a non-hydrolytic base should be employed to do the epimerisation as a separate step before the saponification.

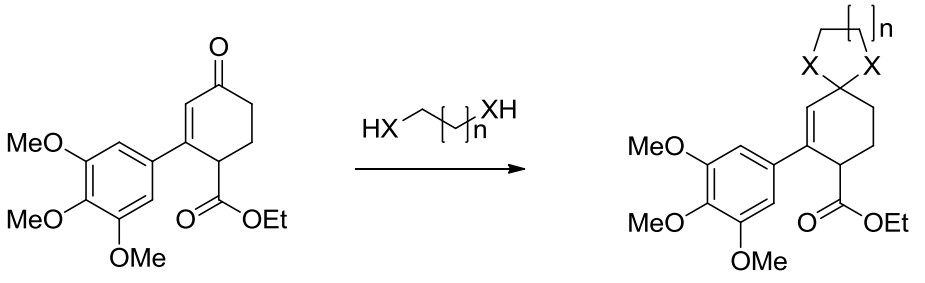
The cyclisation of acid **231** was attempted using DPPA and Et_3N in toluene and after treatment with $BF_3{\cdot}OEt_2$, the demethylated lactam **232** was isolated in 6 % yield. Hydrolysis of the BF_2-adduct using NaOH in EtOAc was omitted and this may have lead to the low yield. This result does show that removal of the conjugated system does allow rearrangement and cyclisation, however further work would need to be carried out to optimise this approach.

227 **232**

Reagents and conditions: a) DPPA, Et_3N, toluene, 90 °C, b) $BF_3{\cdot}OEt_2$

Scheme 73: Cyclisation and demethylation of acid 231

Protecting the carbonyl as either an acetal **227** or a dithioketal **228** was considered for removing the conjugated system as this approach protects the ketone without changing its oxidation state, leaving a handle to further functionalise the C-ring (Scheme 74).



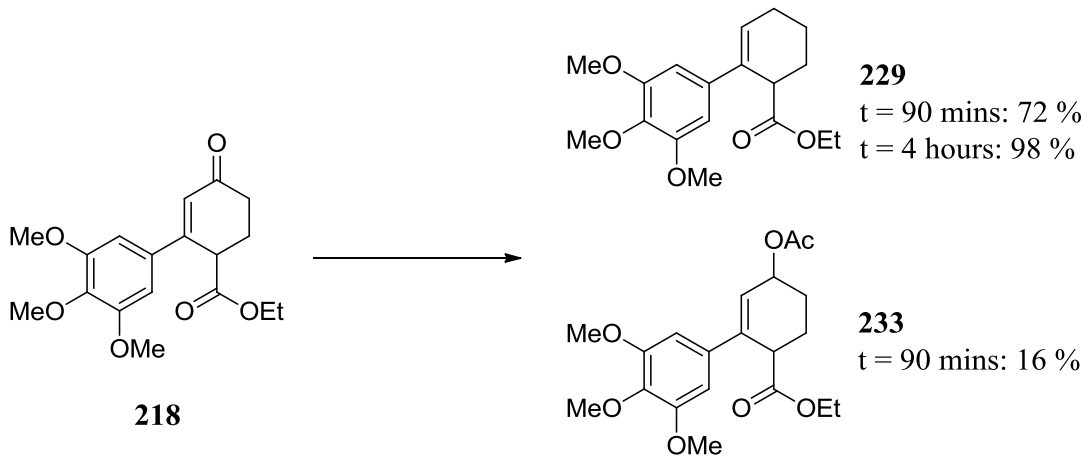
227: X = O, **228**: X = S
n = 1 or 2

Scheme 74: Acetal/dithioacetal protection of a ketone

Acetal protection is a common strategy used to mask ketones,[161] performed under dry acidic conditions, for example *p*-TsOH or pyridinium para-toluenesulfonate in refluxing benzene as reported by Carreño *et al.*,[162] and Murakata *et al.*,[163] or oxalic acid in acetonitrile as reported by Kadas *et al.* in the synthesis of a narciclasine analogue.[164] Deprotection is also straightforward using aqueous acid,[162] which causes a problem with this strategy as the acetal would not be stable to the acidic conditions in the work up for the saponification. The dithioketal protecting group is more robust so would withstand the acidic conditions. [165] The protection can be performed under Lewis acidic conditions as described by Craig *et al.*,[166] and Muthuisamy *et al.*,[167] but taken off under oxidative conditions as reported by Shi *et al.*,[168] and Wu *et al.*.[169] Although this strategy was not investigated it provides a robust method of masking the ketone without complete removal.

The route that has been most successful thus far is the complete removal of the ketone using sodium borohydride and trifluoroacetic acid. The method and conditions were first described by Gribble *et al.* in 1977 during his work on sodium borohydride reductions in acidic media,[170] but has been applied selectively reduce unsaturated ketones as described by Winterfeldt *et al.*,[171] Hanson *et al.*,[172] De Riccadis *et al.*,[173] and Bayón *et al.*.[174] The mechanism is believed to proceed via a stabilized cationic species which is then quenched by the hydride.

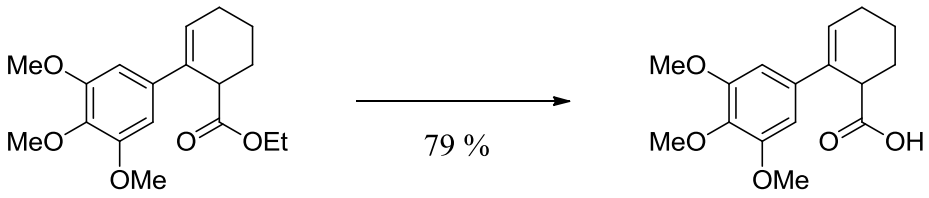
Following the procedure reported by Bayón *et al.*, the complete reduction of the ketone **218** was achieved in 98 % yield after 4 hrs (Scheme 75). Interestingly, after only 90 mins, two products were isolated from the reaction, cyclohexene **229** in 72 % yield and acetate **233** in 16 % yield. The acetate **233** may be an intermediate in the reaction; however it is not known whether its substitution by a hydride occurs via an S_N1 or S_N2 process.



Reagents and conditions: CF_3CO_2H, CH_3CO_2H, $NaBH_4$, CH_3CN, CH_2Cl_2, 1.5-4 hrs

Scheme 75: Reduction of 218 to cyclohexene 229 and acetate 233

Saponification of ester **229** was attempted with $LiOH.H_2O$, but only the starting material was isolated. Instead the ester was hydrolysed using aqueous NaOH heated to reflux giving acid **234** in 79 %, yield as the precursor for the Curtius rearrangement and cyclisation (Scheme 76).

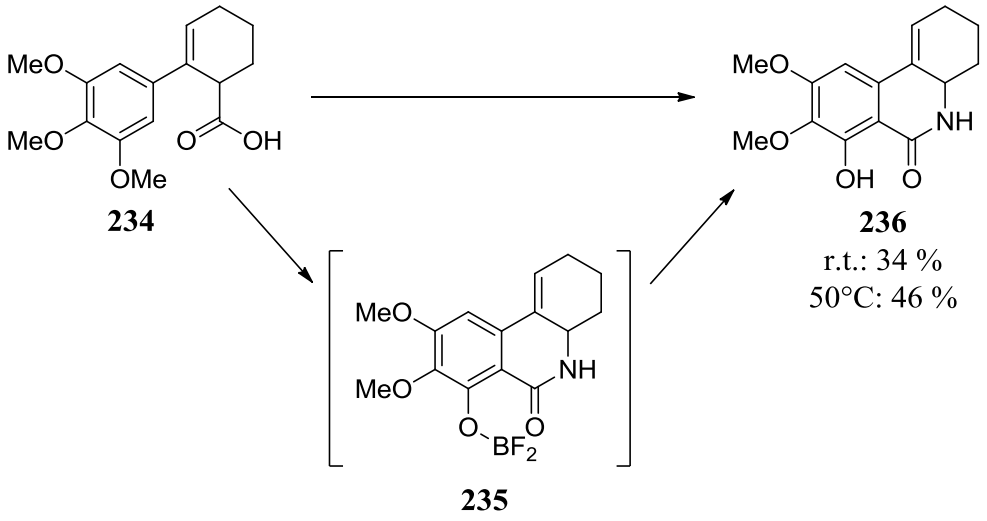


Reagents and conditions: NaOH, H_2O, reflux.

Scheme 76: Saponification of the ester 229

Following the cyclisation procedure optimised on the AB-ring analogues (Section 2.1.1, p. 39), the acid **234** was heated with DPPA and Et_3N in toluene, then the reaction mixture was treated with $BF_3{\cdot}OEt_2$ at room temperature (Scheme 77). The reaction proceeded smoothly; evolution of gas during the reaction with DPPA and precipitation of a solid believed to be the BF_2-adduct **235** during the Lewis acid mediated step were observed. After heating the mixture in 2M NaOH and EtOAc at 50 °C, the cyclised and demethylated product **236** was isolated in a 34 % yield.

When the $BF_3 \cdot OEt_2$ step was performed at 50 °C, the product **236** was isolated in a slightly improved 46 % yield. The remainder of the mass balance was not identified in either of the reactions.



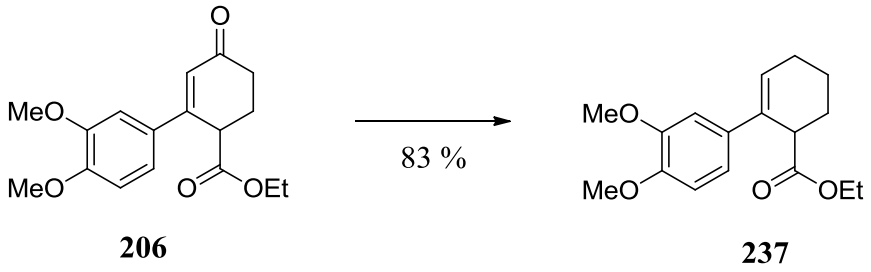
Reagents and conditions: a) DPPA, Et_3N, toluene, 90 °C; b) $BF_3 \cdot OEt_2$, r.t. or 50 °C; b) NaOH, 50 °C

Scheme 77: Synthesis of phenanthridone 236 by the cyclisation and demethylation of acid 234

The 8,9-dimethoxy-7-hydroxyphenanthridone **236** was synthesised in an overall 18 % yield and 6 steps. Despite further optimisation being required, the route was applied to the synthesis of the 8,9-dimethoxyphenanthridone.

3.3. SUCCESSFUL SYNTHESIS OF THE 8,9-DIMETHOXYPHENANTHRIDONE 239

The synthesis of the dimethoxy analogue was resumed at Hagemann's ester **206**. Reduction of the ketone to afford cyclohexene **237** proceeded efficiently, affording the product in 83 % yield after 4 hrs (Scheme 78).

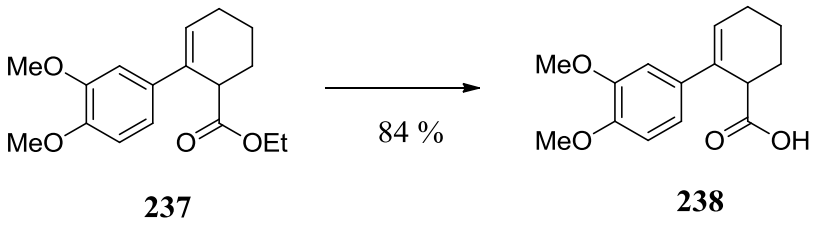


206 **237**

Reagents and conditions: CF_3CO_2H, CH_3CO_2H, $NaBH_4$, CH_3CN, CH_2Cl_2, 4 hrs.

Scheme 78: Reduction of ketone 206 to cyclohexene 237

The ester **237** was then hydrolysed using aqueous NaOH heated at reflux and the acid **238** was isolated in 84 % yield (Scheme 79).

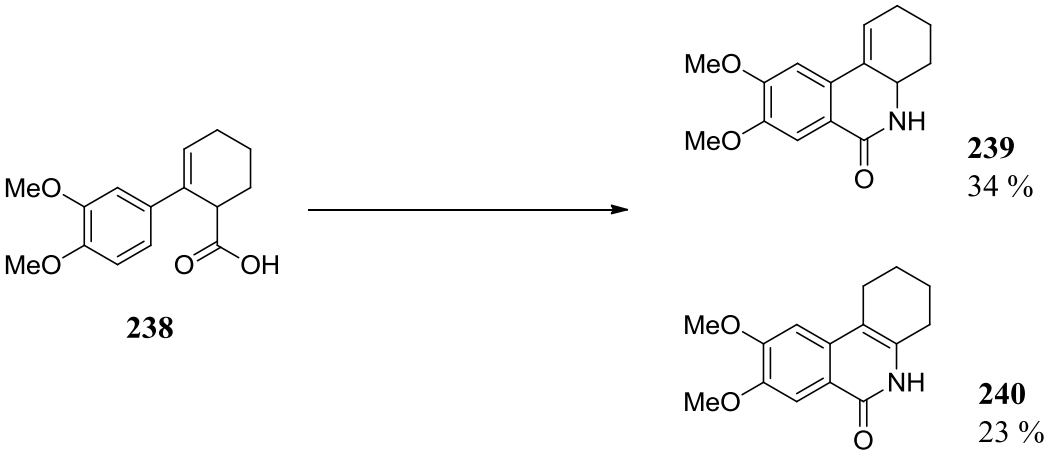


237 **238**

Reagents and conditions: NaOH, H_2O, reflux

Scheme 79: Saponification of ester 237

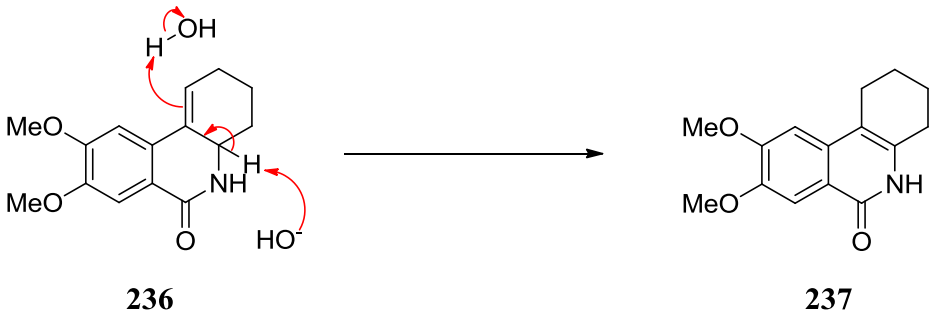
Following the procedure for the cyclisation of 3-(3,4-dimethoxyphenyl)propionic acid **146**, acid **238** was heated at reflux with DPPA and Et_3N in toluene, before treatment with $BF_3{\cdot}OEt_2$ at 50 °C. After heating the reaction mixture in NaOH and EtOAc at 50 °C, two products were isolated from the reaction; the lactam **239** in a 34 % yield and another cyclised product **240** in 23 % yield (Scheme 80). There was also a 28 % yield of a mixture of products **239** and **240**, in a ratio of 31:69, which were not separated by column chromatography, giving a total yield of 85 % of cyclised products.



Reagents and conditions: a) DPPA, Et_3N, toluene, 90 °C; b) $BF_3 \cdot OEt_2$, 50 °C; c) 2M NaOH, EtOAc, 50 ºC

Scheme 80: Cyclisation of the dimethoxy- substituted acid 238 to furnish phenanthridones 239 and 240

The product **240** was formed by the migration of the double bond to the B/C ring junction, to give the more thermodynamically stable tetra-substituted alkene. It is not known at what point the migration occurred, however the migration may proceed by a base catalysed mechanism (Scheme 81).

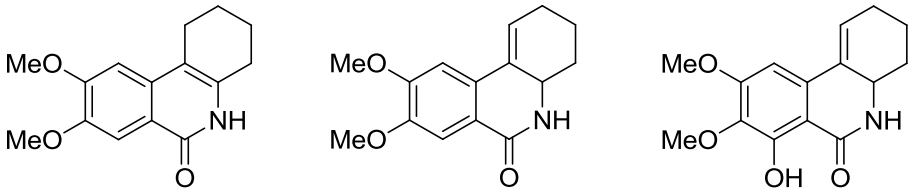


Scheme 81: Base catalysed double bond migration

Phenanthridone **239** was synthesised in an overall yield of 15 % and **240** was synthesised in an overall yield of 10 %. The synthesis was performed in only 6 steps and the final step produced two interesting analogues. Through further optimisation of this reaction, either of the products might be accessed selectively. The synthesis of these analogues has tested the scope of this synthetic route and following further optimisation other interesting analogues may be synthesised using this short route in good yields.

3.4. BIOLOGICAL EVALUATION

The three compounds have been tested in an MTS cell proliferation assay using human HT29 colon cancer cells with 72 hrs exposure time. The compounds have been tested twice and an average taken.



240 17 μM | **239** 37 μM | **236** 23 μM

Figure 37: Biological activity of phenanthridones 236, 239 and 240

The analogues displayed activities in the lower micromolar range (Figure 37). Addition of the C-ring to the molecule increased the activity when compared to the AB-ring analogues (Section 2.3, p. 52). Inclusion of the 7-hydroxyl also increases activity from 37 μM to 23 μM, in keeping with the SAR patterns in the natural product. Interestingly, the compound **240** where the double bond has migrated shows only a 15-fold difference to the natural product **14** where the B/C ring junction is a double bond. This indicates that in this molecule, oxygenation in the C-ring is less important for biological activity. When the double bond sits between the 10b and 1 position, there is approximately a 250-fold difference in activity between **239** and 7-deoxy narciclasine **4**; and 1500-fold difference between **236** and narciclasine **3**.

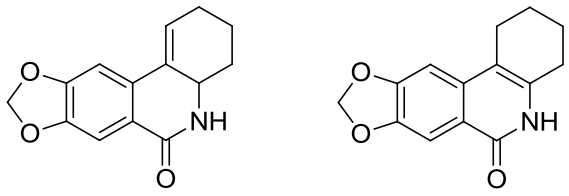
This increase in activity with increasing size of the molecule brings confidence that with the introduction of oxygenation, or other polar and hydrogen bonding groups onto the C-ring, nanomolar activities may be achieved.

3.5. CONCLUSIONS AND FUTURE WORK

3.5.1. Chemistry

A 6-step route to the ABC-ring tricyclic core has been developed using a Robinson annulation and a Curtius rearrangement and intramolecular Friedel-Crafts acylation as key steps in the synthesis. Using this approach 8,9-dimethoxy-7-hydroxyphenanthridone **236** was synthesised in 18 % overall yield and 8,9-dimethoxyphenanthridone **239** was isolated 15 % overall yield. In addition, phenanthridone **240** was isolated in 10 % overall yield after the in-situ isomerisation of the double bond in **239**.

This route can now be applied to the synthesis of the 8,9-methylenedioxyphenanthridone **241**, to further test the scope of the route and access the third substitution pattern that was investigated in the AB-ring analogues. As **240**, the product of double bond migration was active in the HT29 cells, the conditions under which this occurred should be investigated further so either of the regioisomers **241** or **242** can be synthesised selectively.



241 **242**

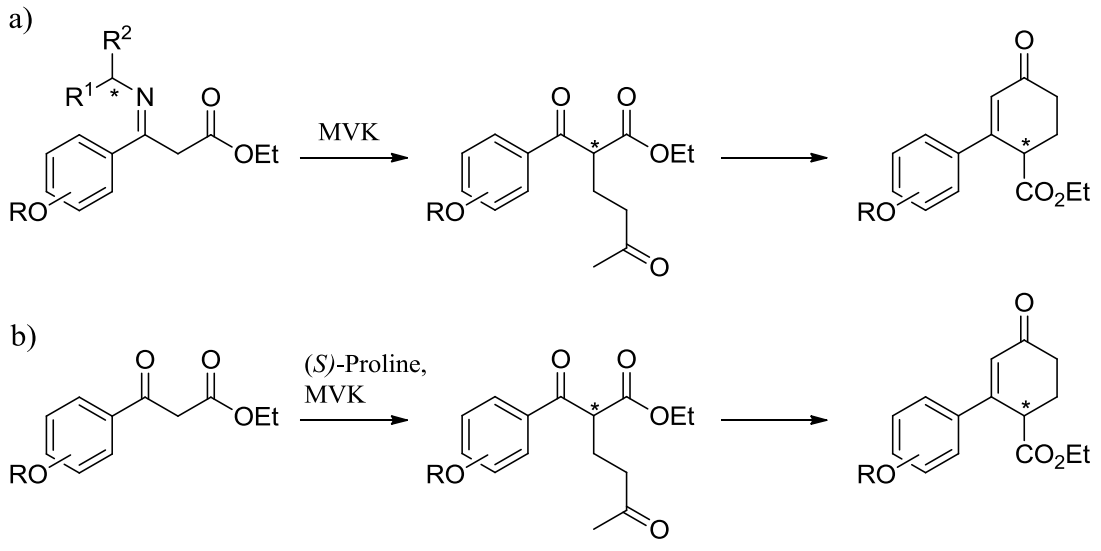
Figure 38: 8,9-(Methylenedioxy)phenanthridone analogues 241 and 242

A number of the steps within the route require further optimisation. The cyclisation of the Michael addition products using *p*-TsOH in refluxing toluene proved to be inefficient when performed on larger scales. Further investigations into pyrrolidine/AcOH as the catalysts for reaction may provide the cyclised product in better yields. It was originally envisaged that the Robinson annulation would be performed in one step. On reflection, it might be possible to develop the K_2CO_3/MeCN conditions for the Michael addition, heating the reaction once the addition has completed to give the cyclised product. Using *t*-BuOK in *t*-BuOH has been described for the annulation and could also be investigated.[175] This is a bulky,

non-nucleophilic base with the larger potassium cation which would not cause the problems of chelation observed with the sodium alkoxide bases discussed in section 3.1.3 (p. 61).

The cyclisation of **234** to give the 8,9-dimethoxy-7-hydroxyphenanthridone **236** also requires further investigation to increase the yields from 42 %. In a similar manner to the dihydroisoquinolinone **151**, it may be possible to isolate and purify the BF_2-adduct then perform the hydrolysis to increase the yield.

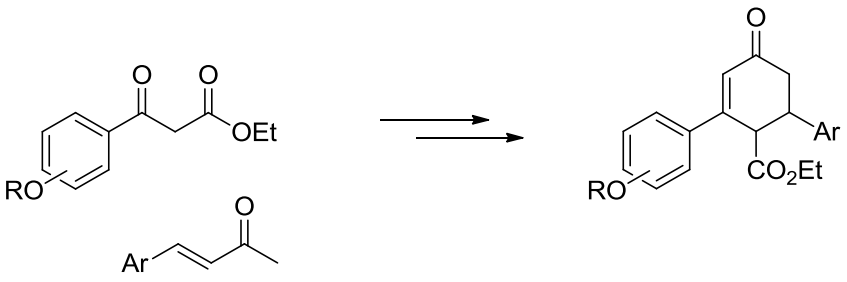
Narciclasine contains a stereogenic centre at the 4a position, so the stereoselective synthesis of its analogues should be investigated. The configuration of the 4a position can be fixed in the Robinson annulation. Methods of achieving this were discussed in the introduction to the Robinson annulation (Section 1.4, p. 27) and can be investigated for these compounds. These include the initial synthesis of a chiral enamine followed by the Michael addition and cyclisation reactions, as was reported in the synthesis of Saudin (Scheme 82a).[80] Alternatively, proline catalysts can be investigated, either in a two-step procedure to perform the cyclisation of the Michael addition product, or to perform the annulation in one step as has been described as Barbas III[98]and Swamainathan[99] (Scheme 82b).



Scheme 82: Methods of performing the Robinson annulation stereoselectively

Narciclasine contains a 2,3,4-trioxygenated C-ring, so the synthesis of analogues with a functionalised C-ring should also be investigated. Originally, the

target compounds contained a ketone in the C-ring which would have provided a handle to introduce other functional groups; however this was removed to aid the Curtius rearrangement. Allylic oxidation of the analogues synthesised in this project can be investigated to reinstall the ketone. Dithiane protection of the ketone was discussed in Section 3.2.3 and this could be investigated as a method of retaining the ketone allowing modification to be made to the ring after the formation of the lactam. Alternatively, the modifications could be made on the Hagemann's ester, prior to the cyclisation of the B-ring. Other possible methods of adding functionality to the ring include the use of enolate chemistry as was discussed in section 1.2 (p. 20). Functionality could also be introduced through the use of different vinyl ketones, for example, methyl styryl ketones would lead to an aryl ring at the 4-position (Scheme 83).



Scheme 83: Introduction of functionality in the C-ring through the use of different vinyl ketones

3.5.2. Biology

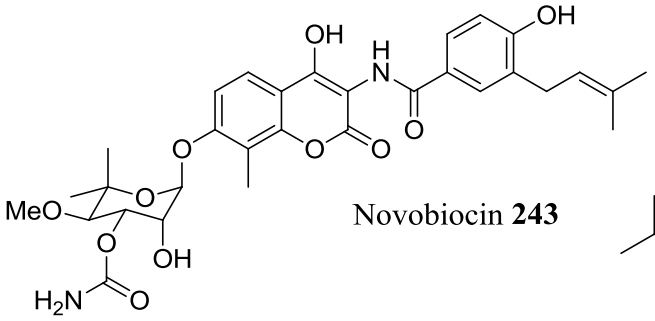
As the cytotoxicity of the analogues has been evaluated against the human colon cancer cell line, the most active compounds should be assessed against other cancer cell lines to assess the consistency of their activity. The human prostate cancer cell line LNCaP and the human breast cancer cell line MDA-MB-231 have been used to test other compounds synthesised within the research group. These additional cell lines have been chosen as they can be easily transferred into *in-vivo* models, allowing *in-vivo* and *in-vitro* results to be easily compared. The selectivity of the most active compounds should also be assessed and this can be done testing them against a FEK-4 skin fibroblast cell line.

4. PRENYLATION OF ELECTRON-RICH ARENES

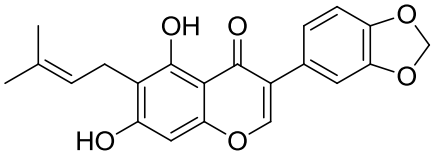
4.1. INTRODUCTION

4.1.1. The Prenyl Group

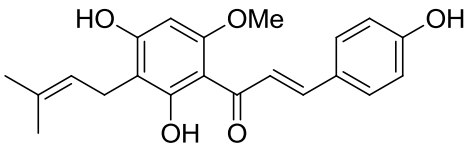
The prenyl group is a motif commonly found in natural products and biologically-active molecules,[176] for example; novobiocin **243**[177] and derrubone **244**[178] have anti-tumour activity though inhibition of heat-shock protein 90 (Hsp90); Xanthohumol **245** has anti-inflammatory activity and anti-cancer activity;[179] and isobavachalcone **246** induces apoptosis and inhibits tumour promotion.[180] It has been shown that prenylation can increase the lipophilicity and activity of a compound;[181] however, the position of the prenyl group is more important than the quantity.[176]



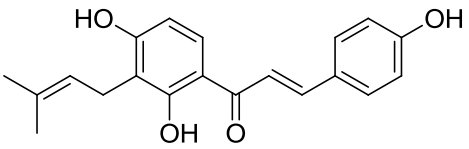
Novobiocin **243**



Derrubone **244**



Xanthohumol **245**

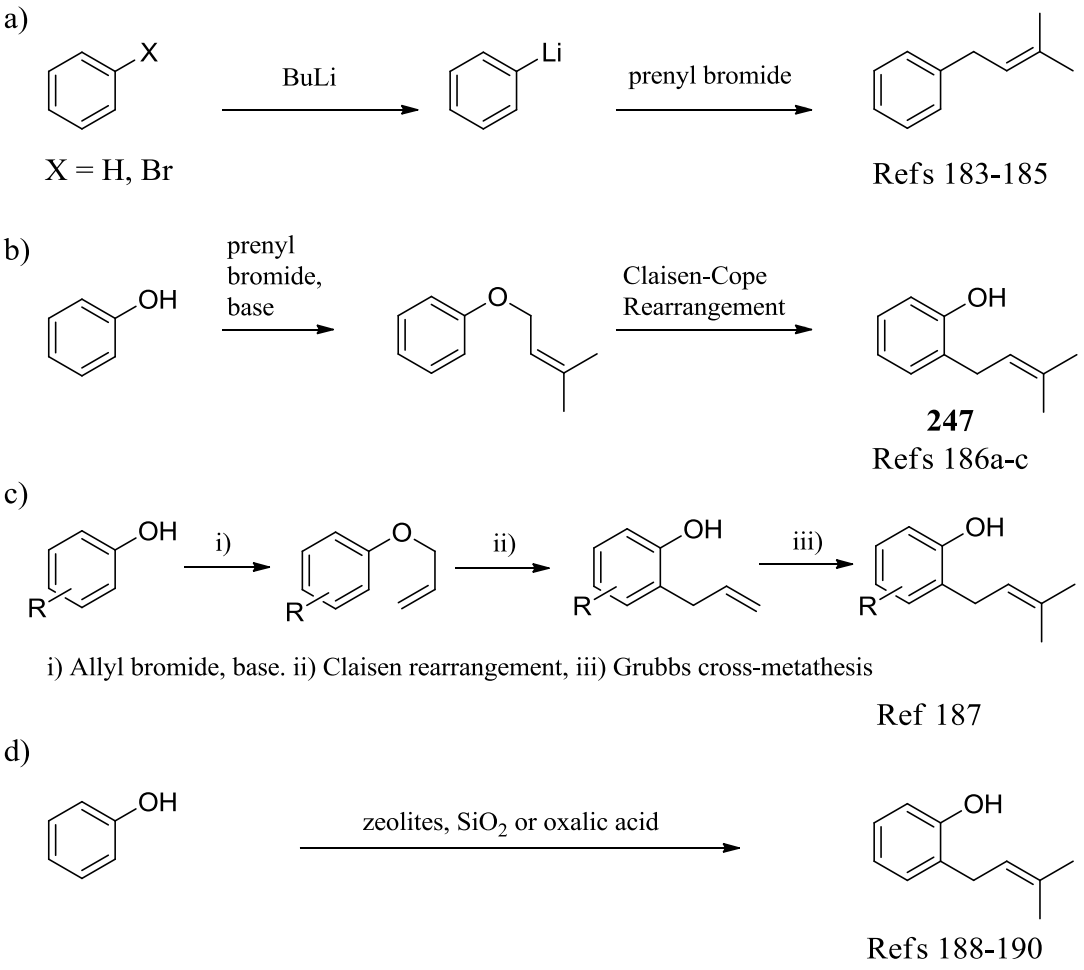


Isobavachalcone **246**

Figure 39: Prenylated biologically active natural products

There have been a number of reported methods of introducing the prenyl group to an arene (Scheme 84). A comprehensive review of *ortho*-prenylation of phenols was published in by Hoarau and Pettus.[182] A common approach is to use lithium-halogen exchange or deprotonation/lithiation of an arene, followed by reaction with prenyl bromide (Scheme 84a). This approach has been applied to the

prenylation of phenols,[183] benzenes,[184] and indoles.[185] Phenol is able to provide a useful handle for prenylation; as it can be O-prenylated, which upon a Claisen-Cope rearrangement gives the *ortho*- or *para*- C-prenylated phenol derivative (Scheme 84b).[186a-c] In the synthesis of **247**, a phenol derivative was O-allylated and after a Claisen rearrangement to afford the *ortho*-allyl material, Grubbs metathesis was used to install the gem-dimethyl group at the terminal end of the double bond (Scheme 84c).[187] Direct C-prenylation of a phenol has been achieved under acidic conditions using zeolite catalysts at high temperatures;[188] a silica mediated process;[189] and by using oxalic acid in refluxing dioxane (Scheme 84d).[190] However, these conditions have only been applied to phenols, so the challenge remains to efficiently prenylated other arene rings.



Scheme 84: Methods of aryl prenylation

4.1.2. The Chroman Group

Like the prenyl group, chroman is also a biologically important motif found in many natural products and medicinally interesting compounds such as Vitamin E **248**;[191] cytotoxic and anti-plasmodial xanthones **249**;[192] anti-mycobacterial dihydrobenzopyrans **250**;[193] and the Dorsmanins A **251**[194] and B **252**.[195]

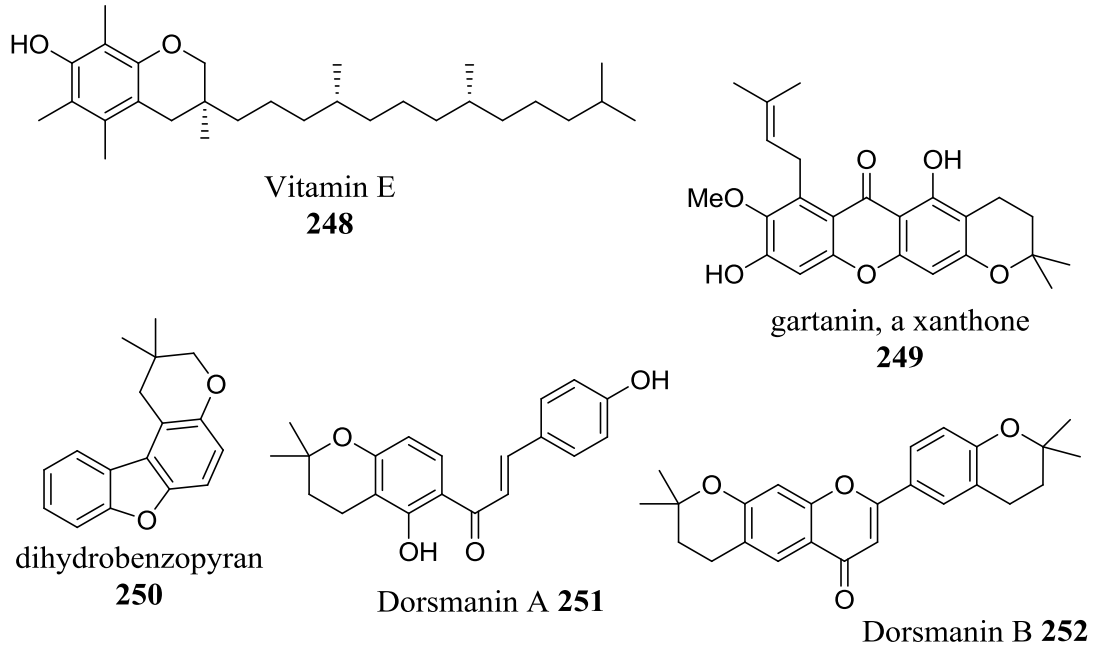
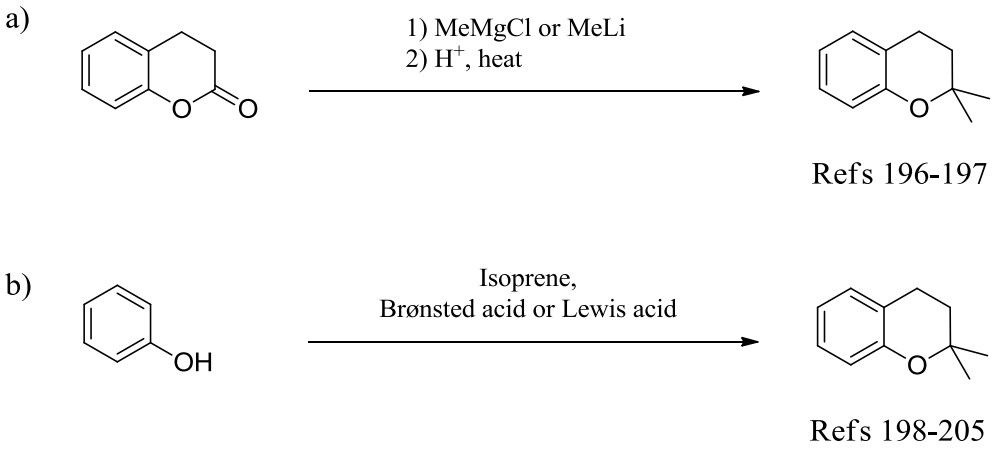


Figure 40: Biologically active chromans

The main approaches to the synthesis of the chroman motif include nucleophilic addition of a Grignard reagent to the corresponding coumarin (Scheme 85a);[196,197] or addition and cyclisation of a prenyl group with a phenol in the presence of a catalyst (Scheme 85b). There have been a number of reported methods of implementing the second approach. Claisen reported the condensation of phenol and isoprene in 1921,[198] then interest in the transformation resumed in the late 1950's and early 1960's when Bader *et al.* reported the use of phosphoric acid[199] and Dewhirst *et al.* reported the use of aluminium phenoxide[200] to catalyse the addition and cyclisation of isoprene with phenol. In a similar manner to that reported by Bader, Ahluwalia *et al.* reported the use of *ortho*-phosphoric acid to catalyse the reaction of isoprene and a phenol in good yields.[201] More recently Lewis acids have been explored as catalysts for the transformation. Montmorillonite clays;[202] a

scandium triflate/ionic liquid system,[203] a copper triflate-bipyridyl complex;[204] and most recently $BF_3 \cdot OEt_2$[205] have all been shown to catalyse the reaction.



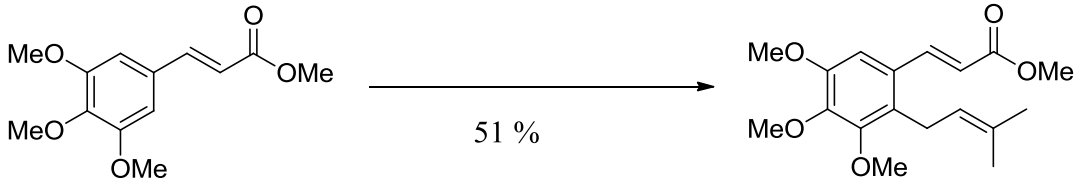
Scheme 85: Synthetic approaches to the chroman ring

4.1.3. Bismuth (III) Triflate

Bismuth (III) triflate is a mild, safe and easily handled Lewis acid that has proved to be useful in many chemical transformations, as reviewed by Gaspard-Iloughmane,[206] and Antoniotti.[207] Recent applications of $Bi(OTf)_3$ as a catalyst include: acetylation of alcohols;[208] esterifications;[209] oxa-Pictet-Spengler reactions;[210] Fries and Claisen rearrangements;[211] Mannich reactions [212,213] and aldol reactions.[214] These papers also discuss the mechanism of action of $Bi(OTf)_3$, describing it as a safe and convenient source of triflic acid which is the actual catalyst in the reaction.

4.2. OPTIMISING THE REACTION CONDITIONS

During our investigations, bismuth (III) triflate was found to catalyse the addition of isoprene to methyl 3,4,5-trimethoxycinnamate (Scheme 86). Due to the biological importance of the prenyl group, the mild reaction conditions and encouraging yield, it was decided that the transformation should be investigated further.

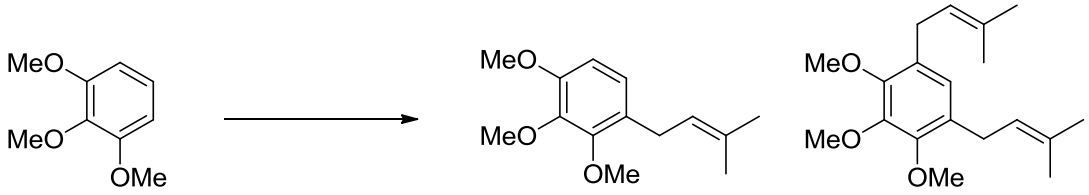


253 **254**

Reagents and conditions: Isoprene, $Bi(OTf)_3$, toluene, r.t., 18 hrs

Scheme 86: Prenylation of methyl 3,4,5-trimethoxycinnamate 253

To optimise the reaction conditions, trimethoxybenzene was used as a model substrate (Scheme 87).



255 **256** **257**

Reagents and conditions: Isoprene, $Bi(OTf)_3$, toluene, 40 °C, 90 mins.

Scheme 87: Prenylation of trimethoxybenzene 252

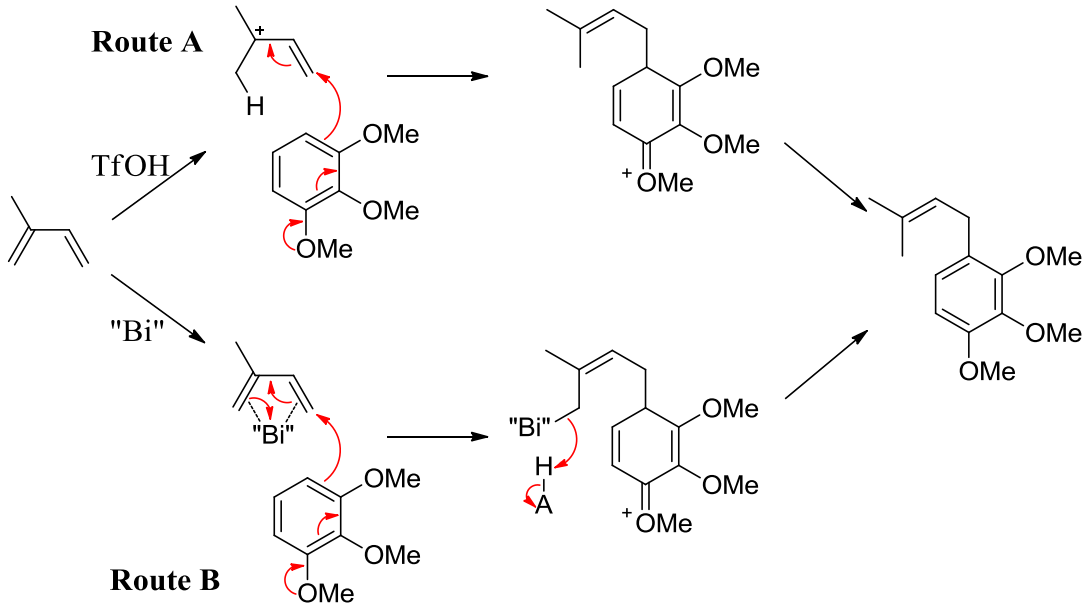
To verify that $Bi(OTf)_3$ was the best catalyst for the transformation, a screen of acids was undertaken on a 0.5 mmol scale. The products were not isolated but the conversion was calculated from the ^1H NMR spectra of the crude material (Table 9). A catalyst was essential for the reaction to proceed (Entry 1) and the protic acid TFA also had no effect on the reaction (Entry 2). Lewis acids $ZrCl_4$ and $AlCl_3$ did not catalyst the prenylation, but degradation of starting materials was observed in the ^1H NMR spectra (Entries 3 and 4). $Yb(OTf)_3$ and $Zn(OTf)_3$ did not catalyse the reaction but degradation of the starting materials was not observed (Entries 5 and 6). Prenylation was observed when $Sc(OTf)_3$ (Entry 7) and $BF_3{\cdot}OEt_2$ (Entry 9) were used; however, $Bi(OTf)_3$ (Entry 8) gave the best result with most of the starting material being consumed and a 70 % conversion to the mono-prenylated product.

Table 9: Screen of Lewis acids for the prenylation reactions

Entry	Acid	% Starting Material 255	% Mono-product 256	% Bis-product 257
1	None	100	-	-
2	TFA	100	-	-
3	$ZrCl_4$	100[a]	-	-
4	$AlCl_3$	100[a]	-	-
5	$Yb(OTf)_3$	100	-	-
6	$Zn(OTf)_2$	100	-	-
7	$Sc(OTf)_3$	58	42	-
8	$Bi(OTf)_3$	11	70	19
9	$BF_3{\cdot}OEt_2$	65	35	-

a: Degradation of the starting material was observed by NMR

Bismuth (III) triflate has been described as a catalyst for many transformations as it has the advantages of being non-toxic and easy to handle. The mode of action of the catalyst has been discussed by both Ollevier[213] and Dumeunier, [215] who believe triflic acid is the active catalyst, which is released upon hydrolysis of $Bi(OTf)_3$ (Scheme 88, route A). An alternative explanation is a bismuth species acts as a Lewis acid and coordinates to the isoprene, activating it towards nucleophilic attack by the aryl ring (Scheme 88, route B).



Scheme 88: Two possible mechanisms for the catalysis of prenylation

The determine the most probable mechanism, a series of reactions were performed on a 2 mmol scale, using 10 mol% $Bi(OTf)_3$ under anhydrous conditions under an inert atmosphere, with a range of different additives (Table 10).

Table 10: Probing the mode of action of $Bi(OTf)_3$

Entry	Additive	Time (hrs)	Yield Starting Material 255 (%)	Yield Mono-Product 256 (%)	Yield Bis-Product 257 (%)
1	Dry solvent and glassware	1.25	0	62	20
2	1 drop (~ 20 μL) water	5	5	63	13
3	33 mol % DTBMP	6	87	7	0
4	"Wet" solvent and glassware	1.5	10	68	23

When the reaction was performed using dried glassware and anhydrous toluene, the mono-product **256** was isolated in 62 % yield after 1.25 hrs in addition to the bis-product **257** in 20 % yield (Entry 1). The reaction was performed with the addition 1 mmol water, a sufficient amount to hydrolyse the $Bi(OTf)_3$ to afford 0.6 mmol TfOH (Entry 2). After 5 hrs the mono-product **256** was isolated in 63 % yield, in addition there was a 5 % yield of the starting material showing that the reaction still proceeds with the addition of water. Following the investigations of Lherbert,[209] the addition of 2,6-di-*tert*-butyl-4-dimethylpyridine (DTBMP) was explored. The bulky base would neutralise and deactivate any triflic acid produced, but leave the bismuth available to act as a Lewis acid. The addition of 33 mol% DTBMP gave an 87 % return of unreacted starting material after 6 hrs (Entry 3), suggesting that the reaction is catalysed by triflic acid liberated by the hydrolysis of $Bi(OTf)_3$. However, addition of too much water can have an adverse effect slowing the reaction down. A sufficient amount of water is introduced to the reaction by the isoprene or $Bi(OTf)_3$ to liberate enough TfOH to catalyse the reaction. The reaction has also been performed using non-anhydrous toluene without drying the glassware and the mono-product **256** was isolated in 68 % yield, with 10 % of the starting material being reclaimed (Entry 4). For consistency of results, the solvent and glassware was dried before being used in subsequent reactions.

The amount of isoprene required for complete conversion of the starting material, with minimum bis-prenylation was also assessed (Table 11). It was found that 1.1 eq. and 1.5 eq. of isoprene were not sufficient to provide full consumption of the starting material (Entries 1 and 2). The best results were obtained using 2 eq. of isoprene (Entry 3), where all the starting material **255** was consumed, but with only a 20 % yield of the bis-product **254**. Increasing the amount of isoprene to 3 eq. lead to an increased yield of the bis-product (Entry 4).

Table 11: Determining the optimal amount of isoprene needed for prenylation

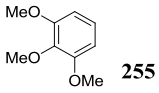
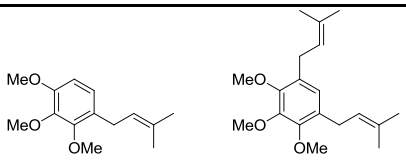
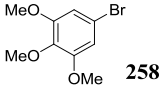
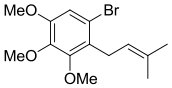
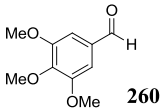
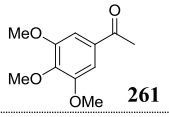
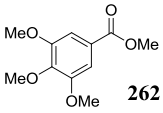
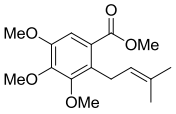
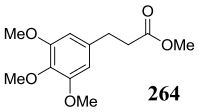
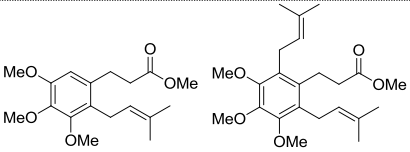
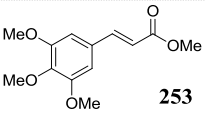
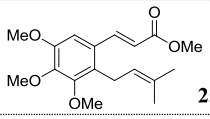
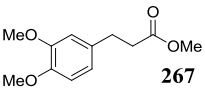
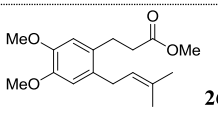
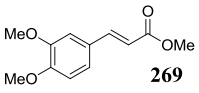
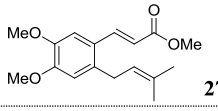
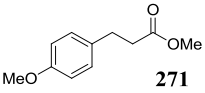
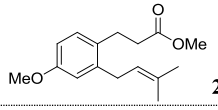
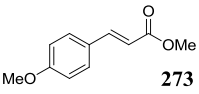
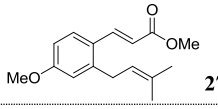
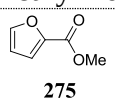
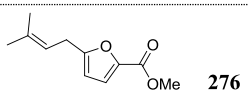
Entry	Equivalents isoprene	Time (hrs)	Yield Starting Material 255 (%)	Yield Mono-Product 256 (%)	Yield Bis-Product 257 (%)
1	1.1	2	22	50	7
2	1.5	1.5	8	65	2
3	2	1.25	0	62	20
4	3	1.25	0	41	36

4.3. SCOPE AND LIMITATIONS

4.3.1. Prenylation of Electron-Rich Aryl Ethers

The optimal reaction conditions for the prenylation of trimethoxybenzene were found to be 2 eq. of isoprene, 10 mol % $Bi(OTf)_3$, in anhydrous toluene at 40 °C in a dried sealed tube under argon. These conditions were applied to a series of substrates to explore the scope and limitations of the reaction (Table 12).

Table 12: Prenylation of electron rich aromatic rings

	Starting material (S.M.)	Product(s)	Time (hrs)	Yield Mono- (%)	Yield Bis- (%)	Yield S.M. (%)
1	 **255**	 **256** **257**	1.25	62	20	-
2	 **258**	 **259**	7	44	-	50
3	 **260**	Complicated mixture of products		-	-	-
4	 **261**	Complicated mixture of products		-	-	-
5	 **262**	 **263**	6	15	-	85
6	 **264**	 **265** **266**	1.5	58	30	-
7	 **253**	 **254**	6	47	-	-
8	 **267**	 **268**	6	64	-	-
9	 **269**	 **270**	6	17	-	57
10	 **271**	 **272**	5	<34[a]	-	56
11	 **273**	 **274**	6	-	-	52
12	Indole		24	-	-	47
13	*N*-Methylindole		24	-	-	49
14	 **275**	 **276**	6	~31[b]		~31[b]

a: The product was synthesised but contained 33 % starting material by ^{1}H NMR analysis which could not be removed by column chromatography. *b*: Obtained as an inseparable mixture by column chromatography in a 1:1 ratio by ^{1}H NMR analysis.

Several trends can be observed in Table 12. Firstly, the more electron donating groups are on the aryl ring, the more efficiently the reaction proceeds; so trimethoxy is better than dimethoxy which is better than monomethoxy. This can be seen when comparing the propionic esters, (Entries 6, 8 and 10) where the yield is significantly reduced when there are fewer methoxy- groups. Secondly, other functional groups on the aryl ring can have a dramatic effect on reactivity. The reactivity of the nucleophilic carbon in the aromatic ring can be gauged by examining the chemical shift of the attached proton in the ^{1}H NMR spectrum. Increasing electron density makes a proton more shielded, reducing its chemical shift. So it follows that the more reactive aryl rings will have protons at a reduced chemical shift (Figure 41).

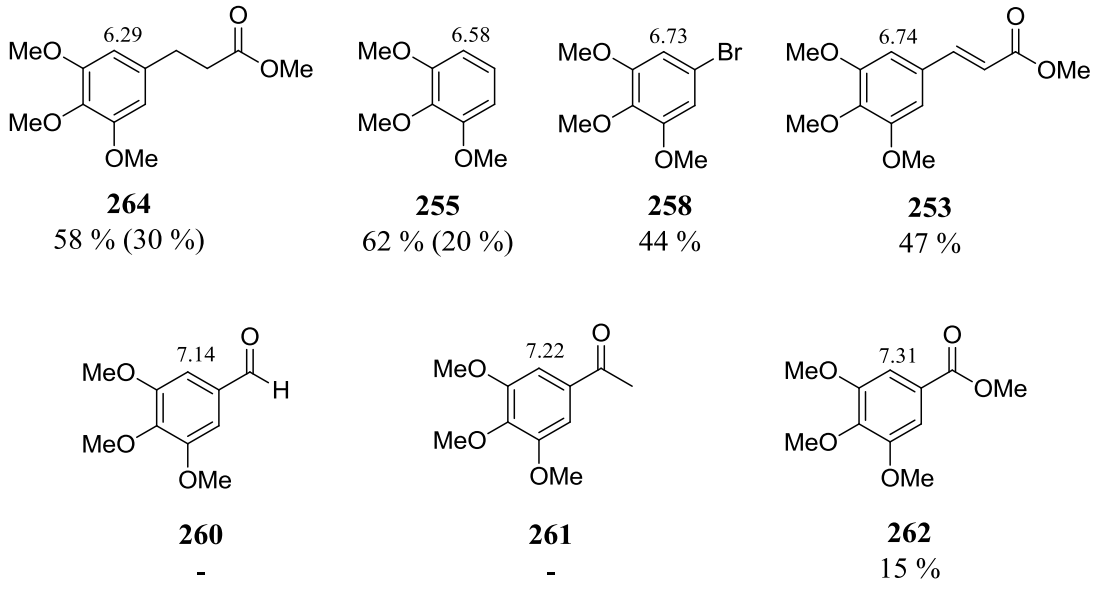


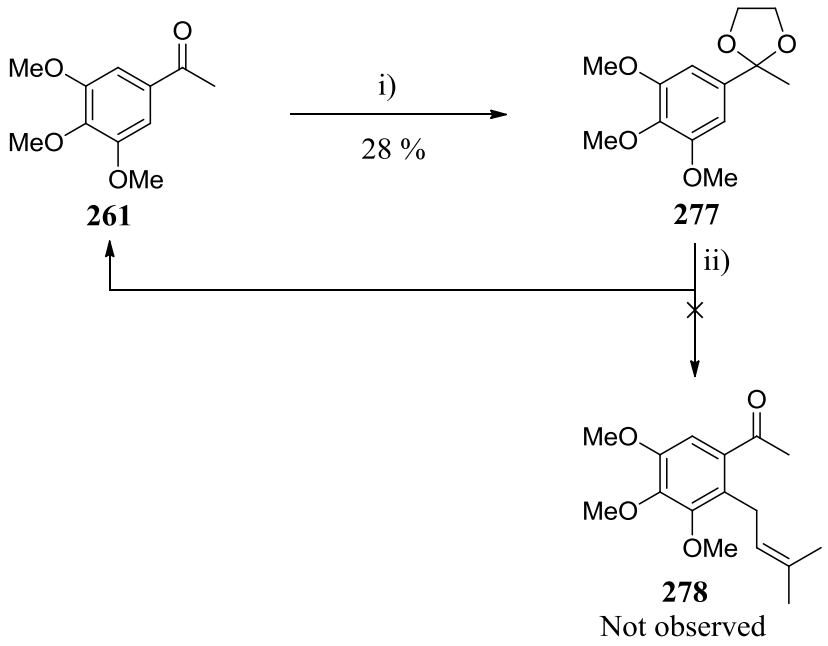
Figure 41: Selected ^{1}H NMR shifts in $CDCl_3$ of protons (ppm) on the electron-rich aromatic rings and the yields of mono-(and bis) products

Trimethoxybenzene **255** (Table 12, entry 1), the bromo-analogue **258** (Entry 2), the propionic ester **264** (Entry 6) and the cinnamic ester **253** (Entry 7) have chemical shifts lower than 7.00 ppm and were all prenylated with modest to good yields, with the bis-prenylated product also being observed in some reactions. The alkyl group of the cinammic ester **253** is slightly electron donating, but the aryl ring is in conjugation with the electron withdrawing ester group giving an overall reduction in electron density and reducing the reactivity of the ring as shown by the

increased chemical shift of 6.74 ppm. This has been translated in the low yield of 47 % and absence of any bis-product (Table 12, entry 7). The bromobenzene **258** was prenylated in only modest yield of 44 % and this may also be due to steric effects of the bulky bromide group (Table 12, entry 2).

Electron-poor aryl rings, where a carbonyl is in direct conjugation with the aromatic ring gave either, in the case of ester **262**, poor yields of product (Table 12, entry 5), or complicated mixtures which could not be separated by column chromatography (Entries 3 and 4). This follows the pattern in the chemical shift of the aryl protons, which is >7.00 in the three compounds. Despite having the highest chemical shift, the ester gave the best yield of prenylated product **263**, whereas prenylated product was not isolated from the reactions with the aldehyde **260** or ketone **261**. This may be due to the difference in reactivity in the carbonyl groups, resulting in side reactions giving complicated mixtures of products. One possible route for these side reactions is the formation of a stabilised benzylic cation resulting from the protonation of the carbonyl by the strong triflic acid. This would also put a positive charge adjacent to the ring, removing the electron density needed to perform the prenylation.

To avoid this, the acetophenone **261** was protected as the acetal **277**, which was then subjected to the prenylation conditions (Scheme 89). $Bi(OTf)_3$ in refluxing THF/H_2O has been described for the deprotection of acetals,[216] however it was anticipated that under the anhydrous acidic conditions, the prenylation would occur swiftly, as was observed with trimethoxybenzene and that deprotection of the acetal would occur slowly, so the prenylated product **278** could be accessed. Following a procedure reported by Kong *et al.*,[217] the acetal **277** was isolated in a poor 28 % yield. When the acetal was submitted to the optimised conditions, the only product observed was the trimethoxyacetophenone **259**. Investigations in this transformation are currently being investigated as the products would be useful starting materials in the syntheses of other medicinally interesting compounds, such as chalones.[218]



Reagents and conditions: i) Ethylene glycol, *p*-TsOH, toluene, reflux, 20 hours; ii) 10 mol% $Bi(OTf)_3$, isoprene, toluene, 40 °C

Scheme 89: Synthesis of acetal protected acetophenone 259 and subsequent attempted prenylation

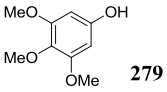
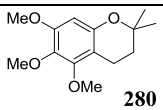
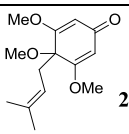
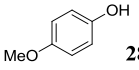
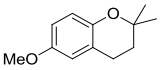
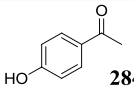
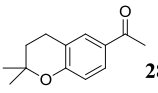
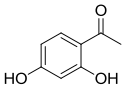
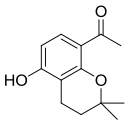
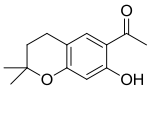
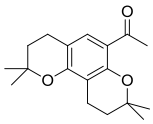
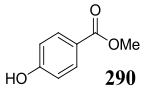
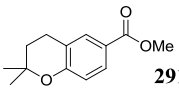
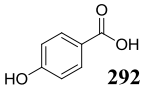
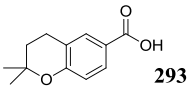
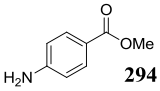
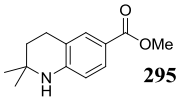
Indole and *N*-methylindole were also investigated as possible electron-rich aromatics for the reaction; however neither of the substrates underwent prenylation. This is despite the compounds containing protons that had chemical shifts of less than 7.00 ppm in the ^{1}H NMR spectrum. The nitrogen atom in indole is not basic, so the lack of reaction is not due to quenching of the triflic acid as was seen with DTBMP in the optimisation reactions. There was some success when the prenylation of furan **275** was investigated, however the product **276** could not be isolated from the starting material, so an accurate yield and characterization could not be obtained. As the furan ring contains a pendant ester group, it is thought the prenylation can be performed in higher yields on more electron-rich furan rings. Further investigations are ongoing to optimise the prenylation of heteroaromatic rings.

4.3.2. Synthesis of Chromans from Phenols

When phenols were examined as electron rich aromatic rings, the product observed in the reactions was a chroman, formed by the cyclisation of the prenylated phenol. As previously discussed, this motif is very common in natural products and

biologically active compounds, so the transformation was explored with a few examples (Table 13).

Table 13: Synthesis of chromans from phenols

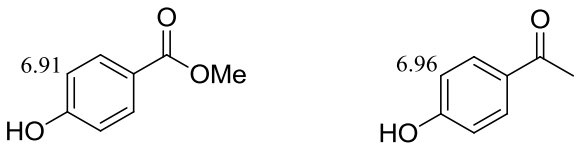
	Starting Material (S.M.)	Product(s)	Time (hrs)	Yield products (%)	Yield SM (%)
1	 **279**	 **280**  **281**	5 18 24[a]	38, 14 55, 26 53, 22	-
2	 **282**	 **283**	2	-	-
3	 **284**	 **285**	5 18	26 58	55 22
4	 **286**	 **287**  **288**  **289**	8	10, 24, 13	
5	 **290**	 **291**	5	65	11
6	 **292**	 **293**	24	3	92
7	 **294**	 **295**	5	0	77

a: Reaction included an aqueous work-up as part of the purification

When trimethoxyphenol **279** was subjected to the reaction conditions for 5 hrs, two products were isolated; the chroman **280** in 38 % yield and the prenylated product **281** resulting from a reaction at the 4-position of the phenol in 14 % yield (Table 13, entry 1). Ketones of similar structure to **281** have been reported previously by Yang *et al.*, so are known to exist in very electron rich systems.[219] Further investigation found that increasing the reaction time greatly increased the yields of both products to 55 % and 26 % respectively after 18 hrs. The addition of a basic work-up to remove the $Bi(OTf)_3$ and break up any complexes formed had no effect on the yield, compared to when the reaction mixture was purified directly by column chromatography. Monomethoxyphenol **282** was also investigated as a substrate and the reaction appeared to have worked by ^1H NMR analysis; however

the low polarity of the product meant that it could not be separated from its contaminants by column chromatography (Table 13, entry 2).

In contrast to the reactions with the benzaldehyde **258** and acetophenone **259**, reactions with phenols containing a ketone or an ester group gave the desired chromans in good yields. When the conditions were applied to 4-hydroxyacetophenone **284** for 5 hrs, the corresponding chroman **285** was isolated in 26 % yield, with a 55 % return of unreacted starting material and degradation products were not observed. In a similar fashion to the reaction with trimethoxyphenol, the yield increased considerably to 58 % when the reaction time was increased to 18 hrs. The resorcinol motif is very common in natural products and the prenyl and chroman derivatives are also seen in nature, so acetophenone **286** was subjected to the reaction conditions. After 5 hrs, three chroman products **287**, **288** and **289** were isolated in 10, 24 and 13 % yields respectively. It was thought that the yields could be improved by increasing the reaction time, but due to the poor regioselectivity of the reaction this was not carried out. The methyl 4-hydroxybenzoate **290** was identified as a possible substrate and this performed very well in the reaction with a 65 % yield of chroman **291** after 5 hrs. These results can also be related to the chemical shifts of the protons on the reacting carbon atoms in the ^{1}H NMR spectra, which are now much lower than in the trimethoxybenzene compounds due to the electron-donating properties of the phenol, showing that the aryl ring is much more reactive (Figure 42).



290 75 %

284 55 %

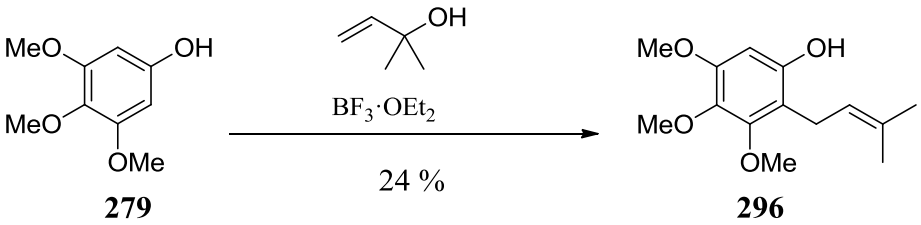
Figure 42: ^{1}H NMR shifts in $CDCl_3$ of protons on the reactive carbons on the phenol ring

4-Hydroxybenzoic acid **292** was also subjected to the reaction conditions as the corresponding chroman has shown to be a potential anti-sickling agent.[220] However, the chroman **293** was prepared in only 3 % after 24 hrs. This could be due to possible coordination of the bismuth to the carboxylic acid, removing more

electron density rendering the aromatic ring less reactive. Electronically, aniline is very similar to phenol, with lone pairs of electrons available for donation into the aromatic ring, so methyl 4-aminobenzoate **294** was subjected to the reaction conditions. The product **295** was not observed and 77 % of the unreacted starting material was recovered. The exact reason for its lack of activity is still unknown; however with a pK_a of approximately 5, similar to that of DTBMP which also has a pK_a of approximately 5, it could be forming a salt with the triflic acid, preventing it from acting as a catalyst.

1.4. APPLICATION TO THE SYNTHESIS OF A NATURAL PRODUCT

The isolation of 2-(3-methyl-2-butenyl)-3,4,5-trimethoxyphenol **296** from *Piper clarkia* was reported in 1994 by Olsen *et al.*,[221] It has been synthesised previously in one-step from trimethoxyphenol **279** and 2-methylbut-3-en-2-ol in 24% yield and its structure was confirmed by X-ray crystallography by Parmar *et al.* [222] It has been shown to possess anti-invasive activity against human breast carcinoma cells.[223]



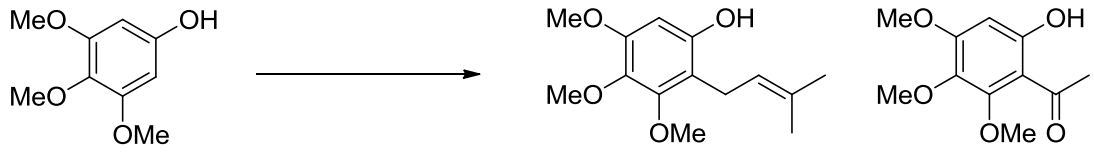
279 **296**

Scheme 90: Current synthesis of 2-prenyltrimethoxyphenol 296[222]

This was an ideal substrate to synthesis using the new methodology access the compound in an improved yield. However as shown in Table 13, prenylation of trimethoxyphenol affords the chroman **280** so a protection strategy was investigated. Acetylation of a phenol in the presence of $Bi(OTf)_3$ has been reported by Mohammedpoor-Baltork.[224] Combining this methodology with our optimised prenylation conditions would provide a one-pot protection and prenylation

procedure. Deprotection could be achieved using the standard conditions potassium carbonate in methanol.[225]

Initially, the reaction sequence was attempted as a one-pot procedure (Scheme 91). The phenol **279** was stirred in toluene with acetic anhydride and $Bi(OTf)_3$ for 15 mins to give the protected phenol. Isoprene was then added to the reaction to perform the prenylation. After 4 hrs the solvent was removed and K_2CO_3 and MeOH were added to give the prenylated phenol. The product **296** was isolated from the reaction, in less than 44 % yield as there were minor impurities which could not be removed by column chromatography. The product of a Fries rearrangement **297** was also isolated in 9 % yield. The catalysis of the Fries rearrangement by $Bi(OTf)_3$ in refluxing toluene has been reported, with reaction times of 1-3 hrs.[226]



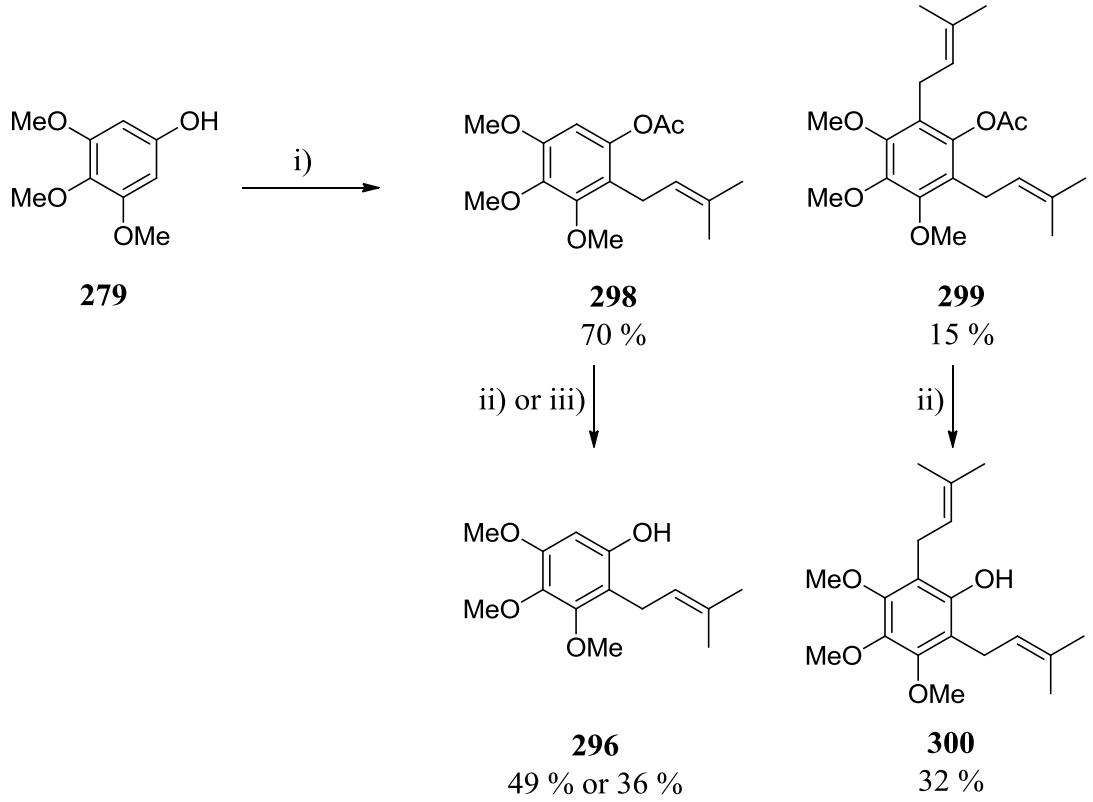
279 **296** <44 % **297** 9 %

Reagents and conditions: a) $Bi(OTf)_3$, Ac_2O, toluene, 15 mins; b) isoprene, 40 °C, 4 hrs; c) K_2CO_3, MeOH, 45 mins.

Scheme 91: Synthesis of 296 in a one-pot procedure

The synthesis was then performed in two steps, isolating and purifying the protected and prenylated phenol **298** before its deprotection (Scheme 92). When the prenylation was left for 4 hrs, the products were observed, but could not be purified sufficiently by column chromatography to obtain accurate yields. However, when the reaction time was reduced to 1 hr, the mono- and bis-prenylated acetates **298** and **299** were isolated in 70 % and 15 % yields respectively. Two strategies were examined for the deprotection of the phenol. Using K_2CO_3 in MeOH as described by Bates[225] gave the mono-product **296** in 49 % yield and the bis-product **300** in 32 % yield. Narendar *et al.*[227] describe the use of NaOAc in $EtOH/H_2O$ for the cleavage of aryl acetates in high yields in the presence of a prenyl group, so this methodology was applied to the deprotection of the monoprenylated acetate **298**. However, the

desired phenol **296** was isolated in only 36 % after 5 hrs. In contrast to the reaction using K_2CO_3, 39 % of the starting material was also recovered.



279

298
70 %

299
15 %

296
49 % or 36 %

300
32 %

Reagents and conditions: i) a) $Bi(OTf)_3$, Ac_2O, toluene, 5 mins; b) isoprene, 40 °C, 1 hr; ii) K_2CO_3, MeOH; iii) NaOAc, EtOH/H_2O.

Scheme 92: Stepwise protection/prenylation and deprotection of trimethoxyphenol

The mono-prenylated phenol **296** was obtained in an overall yield of 34 % from 3,4,5-trimethoxyphenol, higher than the 24 % reported in the reported one-step procedure and the spectroscopic data was consistent with that reported by Olsen *et al.*[221]

4.4. CONCLUSIONS AND FUTURE WORK

A mild procedure has been discovered and developed using bismuth (III) triflate as a catalyst for the prenylation of electron-rich aromatic rings and the synthesis of chromans from phenols. This procedure has been applied to the synthesis of the natural product 2-(3-methyl-2-butenyl)-3,4,5-trimethoxyphenol **296** in 34 % yield over 2 steps.

Further investigations are required to establish why the prenylation of benzaldehydes and acetophenones was not successful and then a solution can be developed. Compounds containing a carbonyl group that is not in conjugation with the aryl ring should be explored as this may establish whether it is the carbonyl group or its conjugation that prevents the reaction from proceeding.

The methodology could also be extended to the prenylation of heterocycles, although investigations and further optimisation will be required for this to establish why the reactions with indole were unsuccessful.

The procedure could also be applied to the synthesis of chroman natural products, such as the dorsmanins **248** and **249**.

As there is evidence that prenylation can increase the activity of a compound, the procedure could also be used to obtain prenylated narciclasine analogues and evaluate their biological activity.

5. EXPERIMENTAL

GENERAL EXPERIMENTAL

Chemicals, solvents and reagents used are commercially available and were used without further purification. Anhydrous solvents were used where indicated.

Glassware for dry reactions was dried either by heating in an oven at 120 °C for at least 1hr, or heating with a hot air gun for 5 mins. The glassware was then allowed to cool under a stream of N_2.

TLC's were carried out on Merck Aluminium backed TLC plates Silica Gel 60 F254 and viewed using UV light of wavelength 254 nm and then stained with potassium permanganate. Merck Silica Gel (0.040-0.063 mm) was used for column chromatography. Compounds were loaded as an oil, CH_2Cl_2 solution or dry loaded by adsorption onto silica.

Melting points were obtained using a Reichert-Jung heated-stage microscope. Infrared spectra were recorded on a Perkin-Elmer Spectrum RXI FT-IR system and all values are recorded in cm^{-1}.

^1H NMR spectra were obtained on JEOL Eclipse (270 MHz), Varian Mercury VX (400 MHz), Bruker Avance III (400 MHz) or Bruker Avance III (500 MHz) spectrometers. ^{13}C NMR spectra were obtained on JEOL Eclipse (67.9 MHz), Varian Mercury VX (100 MHz) Bruker Avance III (100 MHz) or Bruker Avance III (125 MHz) spectrometers. The chemical shifts are recorded in parts per million (ppm) with reference to tetramethylsilane. The coupling constants *J* are quoted to the nearest 0.5 Hz are not rationalised. The multiplicities are assigned as a singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), doublet of doublet of doublets (ddd), doublet of triplets (dt), triplet of doublets (td) and multiplet (m). Pendant NMR data is given after the ^{13}C NMR chemical shifts as +ve (CH and CH_3) and –ve (C and CH_2).

Mass spectra and high resolution mass spectra were obtained on a micrOTOF^{TM} from Bruker Daltonics (Bremen, Germany). This is a Time-of-Flight mass spectrometer coupled with an electrospray source (ESI-TOF). This instrument can be used to measure accurate mass to 5 ppm externally calibrated and 2 ppm internally calibrated. Samples are introduced either by syringe pump or flow

injection using an autosampler in an Agilent 1100 LC system. The instrument is calibrated using a sodium formate solution, which is applicable to both positive and negative ionisation mode. These samples were analysed under standard conditions for small molecules in positive electrospray ionisation mode. The instrument acquires both accurate mass and true isotope patterns, therefore both of these dimensions of information are used to help determine or confirm the molecular formula. Ions are most often present as protonated or sodiated molecules. Data was processed using external calibration with the Bruker Daltonics software, DataAnalysis^{TM} as part of the overall hardware control software, Compass 1.1^{TM}.

Analytical RP-HPLC was performed using a Waters 2695 Alliance module equipped with a Waters 2996 photodiode array detector (210-350 nm). The chromatographic system consisted of a Hichrom Guard column for HPLC and a Phenomenex Synergi 4 µm Max-RP19 column (150 x 4.60 mm), using a gradient of 5 to 65 % 0.1 % TFA in CH_3CN in 0.1 % TFA in MilliQ over 15 mins.

X-ray Crystallography: Single crystals were analysed at 150(2) K using graphite monochromated Mo(Kα) radiation and a Nonius Kappa CCD diffractometer. The structures were solved using SHELXS-97 and refined using SHELXL-97.

5.1. MTS CELL PROLIFERATION ASSAY PROTOCOL

This assay uses a 96 well plate format to determine cell viability and is based on the Promega Cell Titer 96 Aqueous One Solution Cell Proliferation Assay. Seed densities of 500 cells per well were used and final drug concentrations of 500 µM, 200 µM, 100 µM, 50 µM, 20 µM, 10 µM, 5 µM, 2 µM, 1 µM and 500 nM in 1% DMSO. Drugs were incubated with the HT29 cell line for 72 days prior to reading and IC_{50} curves were generated using SigmaPlot 8 software. Each IC_{50} value is the average of at least two independent experiments conducted on separate days.

5.2. SYNTHESIS OF AB-RING ANALOGUES

5.2.1. Synthesis of AB-ring Analogues using the Curtius Rearrangement

General Procedure 1: Preparation and cyclisation of the isocyanate.

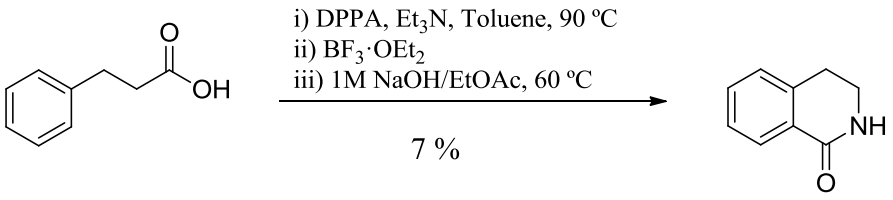
Method A: Following the procedure reported by Kimoto *et al.*,[53] a solution of ethyl chloroformate (475 μL, 5 mmol) in acetone (1.5 mL) was added to a stirred solution of acid (5 mmol) and Et_3N (695 μL, 5 mmol) in acetone/H_2O (7.5 mL, 5:1) at 0 °C open to air and allowed to warm to r.t.. After 1 hr, a solution of NaN_3 (487 mg, 7.5 mmol) in water (1.5 mL) was added in one portion and the reaction stirred for a further 30 mins. Upon dilution with toluene/H_2O (21.8 mL, 4:3) the organic fraction was separated, washed with water, dried with anhydrous $MgSO_4$ and filtered into a dry flask under N_2. The vigorously stirred solution was heated at 90 °C for 45 mins. The solvent was removed *in vacuo* the oil was cooled to 0 °C under N_2 and $BF_3{\cdot}OEt_2$ (2.5 mL) added. The reaction allowed to warm to r.t. and was stirred for 18 hrs, then quenched with saturated aqueous $NaHCO_3$ (25 mL) and extracted with EtOAc (2 x 25 mL). The combined organic fractions were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent removed *in vacuo*. After column chromatography [silica, PE-EtOAc-methanol] the product was isolated

Method B: Following the procedure reported by Kimoto *et al.*,[53] a solution of ethyl chloroformate (475 μL, 5 mmol) in acetone (1.5 mL) was added to a stirred solution of acid (5 mmol) and Et_3N (695 μL, 5 mmol) in acetone/H_2O (7.5 mL, 5:1) at 0 °C open to air and allowed to warm to r.t.. After 1 hr, a solution of NaN_3 (487 mg, 7.5 mmol) in water (1.5 mL) was added in one portion and the reaction stirred for a further 30 mins. Upon dilution with toluene/H_2O (21.8 mL, 4:3) the organic fraction was separated, washed with water, dried with anhydrous $MgSO_4$ and filtered into a dry flask under N_2. The vigorously stirred solution was heated at 90 °C for 45 mins. The solution was then cooled to 0 °C and $AlCl_3$ (2 g, 15 mmol) added. The reaction was allowed to warm to r.t. and was stirred for 18 hrs, then quenched with saturated aqueous $NaHCO_3$. The white solid was removed by filtration through celite and washed thoroughly with EtOAc. The aqueous layer was further extracted with EtOAc (20 mL). All the organic fractions were combined, washed with brine, dried

over anhydrous $MgSO_4$, filtered and the solvent removed *in vacuo*. After column chromatography [silica, PE-EtOAc] the product was isolated.

Method C: Diphenylphosphoryl azide (1.12 mL, 5 mmol) was added to a stirred solution of arylpropionic acid (5 mmol) and anhydrous Et_3N (695 μL, 5 mmol) in anhydrous toluene (15 mL) under N_2 at r.t. then the reaction heated at 90 °C for 90 mins. On cooling the solvent was removed and the flask cooled to 0 °C under N_2. $BF_3{\cdot}OEt_2$ (2.5 mL) was added then the reaction was allowed to warm to r.t. and stirred for 16 hrs. The reaction was quenched to pH 10 with 2M NaOH and diluted with EtOAc (20 mL), then heated at 50 °C for 1 hr. After cooling to r.t. the phases were separated and the aqueous fraction extracted with EtOAc (2 x 20 mL). The combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo*. After column chromatography [silica, PE-EtOAc] the product was isolated.

3,4-Dihydroisoquinolin-1(2H)-one (139)



134 **139**

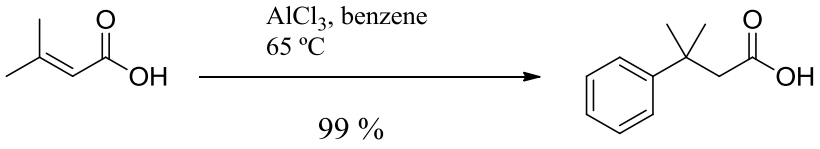
Following general procedure 1C, performing the cyclisation step at 80 °C, dihydrocinnamic acid **134** (750 mg, 5 mmol) gave dihydroisoquinolinone **139** (52 mg, 5 %) as an amorphous solid.

R_f [PE-EtOAc 20:80] 0.20; **^{1}H NMR** δ_H(400 MHz, CD_3OD) 7.94 (1H, d, *J* 8.0 Hz, C(8)H), 7.47 (1H, dd, *J* 8.0 and 8.0 Hz, C(6)H), 7.33 (1H, dd, *J* 8.0 and 8.0 Hz, C(7)H), 7.26 (1H, d, *J* 8.0 Hz, C(5)H), 3.48 (2H, t, *J* 6.5 Hz, C(3)H_2) and 2.96 (2H, t, *J* 6.5 Hz, C(4)H_2); **^{13}C NMR** δ_C(100 MHz, CD_3OD) 168.3− (C1=O), 140.9− (C8a), 133.5+ (C6), 129.8− (C4a), 128.6+ (C5 or C8), 128.4+ (C5 or C8), 128.0+ (C7), 40.8− (C3) and 28.9− (C4); **MS** (+ESI) *m/z* 192 ($M+H^+$, 22 %), 214 ($M+Na^+$,

78) and 405 (2M+Na^+, 100); **HRMS** (+ESI) Found M+Na^+, 214.0476; $C_{10}H_9NO_3Na$ requires $M+Na^+$ 214.0480.

Spectroscopic data is consistent with that reported by Winter *et al.*[228]

3-Methyl-3-phenylbutanoic acid (141)



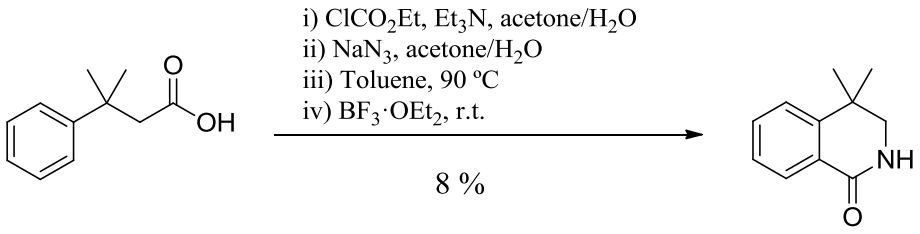
140 **141**

Following the procedure reported by Andersen *et al.*,[229] $AlCl_3$ (1.20 g, 9 mmol) was added to a stirring solution of 3-methylbut-2-enoic acid **140** (292 mg, 2.9 mmol) under N_2 and the reaction heated at 65 °C for 90 mins. The reaction mixture was acidified to pH 1 with conc. HCl and then extracted with EtOAc (3 x 25 mL). The combined organic fractions were extracted with saturated aqueous $NaHCO_3$ (6 x 30 mL), then the combined basic fractions were acidified to pH 1 with conc. HCl and extracted with EtOAc (5 x 50 mL). The combined organic fractions were dried over anhydrous Mg_2SO_4, filtered and the solvent removed *in vacuo* give the product **141** (515 mg, 99 %) as a white solid without further purification.

^{1}H NMR δ_H(270 MHz, $CDCl_3$) 7.38-7.17 (5H, m, C(Ph)H), 2.65 (2H, s, C(2)H_2) and 1.47 (6H, s, CH_3).

Spectroscopic data is consistent with that reported by Andersen *et al.*[229]

4,4-Dimethyl-3,4-dihydro-2*H*-isoquinolin-1-one (142)



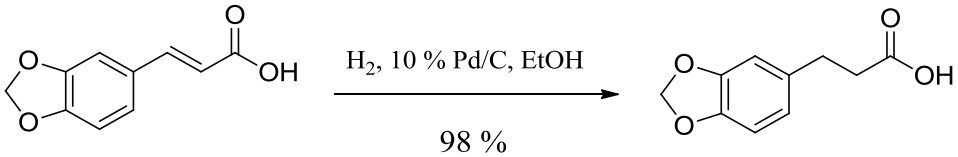
141 **142**

Following general procedure 1A, propanoic acid **141** (483 mg, 2.7 mmol) gave lactam **142** (37 mg, 8 %) as an amorphous solid.

R_f [EtOAc] 0.41; **IR** ν_{max}(thin film) 3322 (NH), 2968, 2931, 2874 (CH), 1701 (C=O), 1530 (Ph) and 1221(CO); **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 8.05 (1H, dd, *J* 8.0 and 1.5 Hz, C(8)H); 7.49 (1H, ddd, *J* 8.0, 8.0 and 1.3 Hz, C(6)H); 7.36-7.29 (2H, m, C(5)H and C(7)H); 6.62 (1H, broad s, N(2)H); 3.30 (2H, d, *J* 2.7 Hz, C(3)H_2) and 1.34 (6H, s, C(4)(CH_3)$_2$); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 166.2− (C1=O), 147.4− (C8a), 132.6+ (C6); 128.2+ (C8), 127.4− (C4a), 126.6+ (C5 or C7), 123.7+ (C5 or C7), 52.3− (C3), 34.2− (C4) and 26.6+ (CH_3); **MS** (+ESI) *m/z* 198 ($M+Na^+$, 58 %) and 373 ($2M+Na^+$, 100 %); **HRMS** (+ESI) Found $M+Na^+$, 198.0884; $C_{11}H_{13}NONa$ requires $M+Na^+$ 198.0895.

Spectroscopic data is consistent with that reported by Ben-Ishai *et al.*[230]

3-(3,4-Methylenedioxyphenyl)propionic acid (143)



143

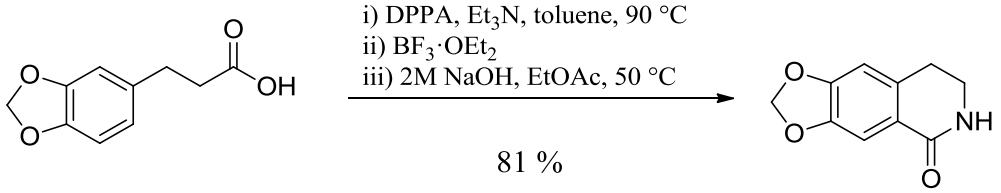
10 % palladium on carbon (208 mg, 0.2 mmol) was added to a vigorously stirred mixture of 3,4-methylenedioxycinnamic acid (2 g, 10.4 mmol) in EtOH (50 mL). After 3 cycles of purging the flask with N_2 then a vacuum, the flask was put

under an atmosphere of H_2. After 2 hrs, the mixture was filtered through celite, washing thoroughly with EtOH, then the solvent removed *in vacuo* to afford the propionic acid **143** (1.97 g, 98 %) as a white solid without further purification.

^{1}H NMR δ_H(400 MHz, $CDCl_3$) 8.60 (1H, broad s, OH), 6.74-6.64 (3H, m, C(Ar)H), 5.92 (2H, s, OCH_2O), 2.87 (2H, t, *J* 8.0 Hz, C(3)H_2) and 2.63 (2H, t, *J* 8.0 Hz, C(2)H_2); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 178.6, 147,7, 146.0, 134.0, 121.1, 108.8, 108.3, 100.9, 35.9 and 30.4.

Spectroscopic data is consistent with that reported by Haga *et al.*[231]

7,8-Dihydro-6*H*-[1,3]dioxolo[4,5-*g*]isoquinolin-5-one (144)



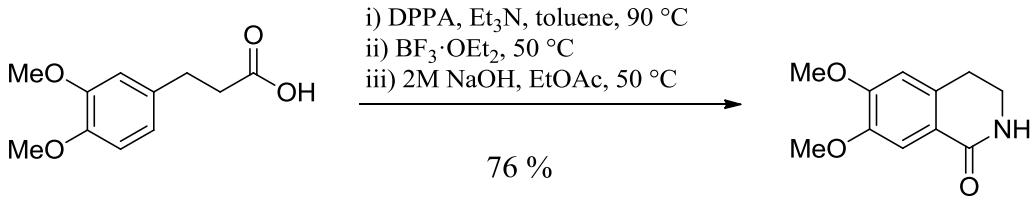
143 **144**

Propionic acid **143** (970 mg, 5 mmol) gave, following general procedure 1A lactam **144** (598 mg, 63 %); and following general procedure 1C gave lactam **144** (772 mg, 81 %) as a white solid.

R_f [PE-EtOAc 20:80] 0.20; **Mp** 185-187 °C (from EtOAc); lit.,[232] 187-187.5 °C (from PhH); **IR** ν_{max}(KBr disc) 3456 (NH), 3188, 3046, 2900 (CH), 1657 (C=O), 1610, 1479 (Ph), 1260 (CO) and 1038; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 7.52 (1H, s, C(8)H), 6.93 (1H, broad s, NH), 6.67 (1H, s, C(5)H), 6.02 (2H, s, OCH_2O), 3.55 (2H, t, *J* 6.5 Hz, C(3)H_2) and 2.91 (2H, t, *J* 6.5 Hz, C(4)H_2); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 166.2− (C1=O), 150.7− (C7-O), 146.8− (C6-O), 134.5− (C8a), 122.8− (C4a), 107.8+ (C8), 107.2+ (C5), 101.4− (OCH_2O), 40.1− (C3) and 28.4− (C4); **MS** (+ESI) *m/z* 192 ($M+H^+$, 22 %), 214 ($M+Na^+$, 78) and 405 ($2M+Na^+$, 100); **HRMS** (+ESI) Found $M+Na^+$, 214.0476; $C_{10}H_9NO_3Na$ requires $M+Na^+$ 214.0480; **HPLC** t_R 9.5 (100 %).

Spectroscopic data is consistent with that reported by Hanaoka *et al.*[232]

6,7-Dimethoxy-3,4-dihydroisoquinolin-1(2H)-one (147)



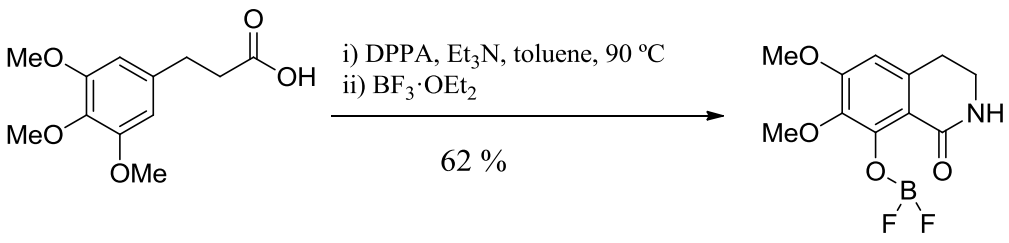
146 **147**

Following general procedure 1C, performing the cyclisation step at 50 °C, propionic acid **146** (1.05g, 5 mmol) gave lactam **147** (784 mg, 76 %) as a white solid.

R_f [EtOAc] 0.11; **Mp** 174-177 °C (from EtOAc); lit.,[233] 173 °C (from PhH/Et_2O); **IR** ν_{max}(KBr disc) 3187, 3044, 2863 (CH), 1656 (C=O), 1603, 1510, 1481 (Ph), 1271 (CO) and 1050; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 7.56 (1H, s, C(8)H), 6.66 (1H, s, C(5)H), 6.36 (1H, broad s, NH), 3.91 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.54 (2H, td, *J* 6.5 and 3.0 Hz, C(3)H_2) and 2.91 (2H, t, *J* 6.5 Hz, C(4)H_2); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 166.4− (C1=O), 152.1− (C7-O), 148.0− (C6-O), 134.5− (C8a), 122.8− (C4a), 110.1+ (C8), 109.5+ (C5), 56.0+ (OCH_3), 56.0+ (OCH_3), 40.4− (C3) and 28.0− (C4); **MS** (+ESI) *m/z* 208 ($M+H^+$, 35 %), 230 ($M+Na^+$, 33) and 437 ($2M+Na^+$, 100); **HRMS** (+ESI) Found $M+Na^+$, 230.0767; $C_{11}H_{13}NO_3Na$ requires $M+Na^+$ 230.0787; **HPLC** t_R 8.6 (100 %).

Spectroscopic data is consistent with that reported by Zhu *et al.*[234]

8-(Difluoroboryloxy)-6,7-dimethoxy-3,4-dihydroisoquinolin-(2*H*)-one (148)

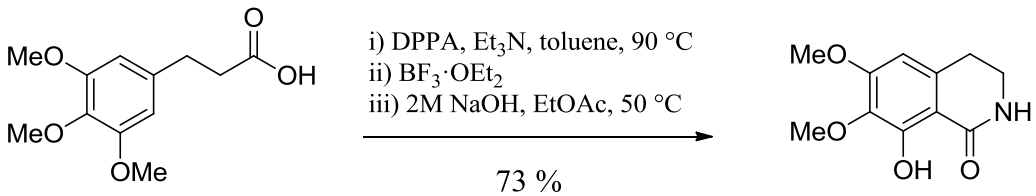


149 **148**

Diphenylphosphoryl azide (5.6 mL, 25 mmol) was added to a stirred solution of arylpropionic acid (6.0 g, 25 mmol) and anhydrous Et_3N (3.5 mL, 25 mmol) in anhydrous toluene (75 mL) under N_2 at r.t. then the reaction heated at 90 °C for 1 hr. After cooling to r.t., the solvent was removed and the flask cooled to 0 °C under N_2. $BF_3{\cdot}OEt_2$ (4 mL) was added then the reaction was allowed to warm to r.t. and stirred for 16 hrs. The reaction mixture was diluted with THF-Et_2O (1:1, 100 mL) and the crude solid product removed by filtration. After recrystallisation from EtOAc, the product (4.2 g, 63 %) was isolated as a white solid.

Mp 237-239 °C (from EtOAc); **IR** ν_{max}(KBr disc) 3326, 3303 (NH), 3027, 2986, 2830, 1656, 1609, 1540, 1489, 1438, 1242, 1132, 1022 and 758; **^{1}H NMR** δ_H(400 MHz, d_6-DMSO) 10.37 (1H, s, NH), 6.68 (1H, s, C(5)H), 3.87 (3H, s, OCH_3), 3.68 (3H, s, OCH_3), 3.59 (2H, t, *J* 7.5 Hz, C(3)H_2) and 2.95 (2H, t, *J* 7.5 Hz, C(4)H_2); **^{13}C NMR** δ_C(100 MHz, d_6-DMSO) 165.7− (C1=O), 159.7− (C6-O or C7-O), 152.6− (C8), 135.2− (C8a), 134.9− (C6-O or C7-O), 103.9+ (C5-H), 101.0− (C4a), 60.1+ (OCH_3), 56.3+ (OCH_3), 39.1− (C3) and 25.1− (C4); **^{19}F NMR** δ_F(376 MHz, d_6-DMSO) −144.24, −144.30; **^{11}B NMR** δ_B(128 MHz, d_6-DMSO) 1.76; **MS** (+ESI) *m/z* 294 ($M+Na^+$, 80 %) and 565 ($2M+Na^+$, 60); **HRMS** (+ESI) Found $M+Na^+$, 294.0726; $C_{11}H_{12}NO_4BF_2Na$ requires $M+Na^+$ 294.0720.

6,7-Dimethoxy-8-hydroxy-3,4-dihydro-2*H*-isoquinolin-1-one (151)



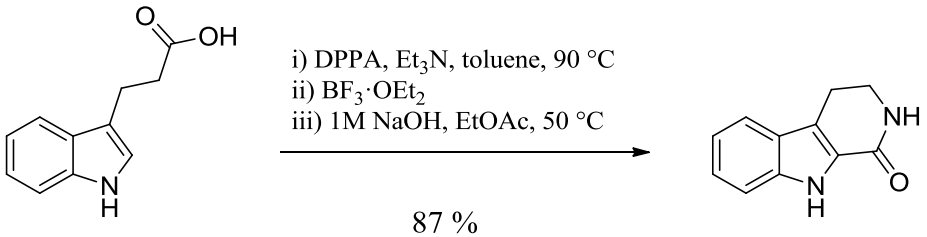
149 **151**

Method A: Following general procedure 1C, propionic acid **149** (1.20 g, 5 mmol) gave isoquinolinone **151** (818 mg, 73 %) and propionic acid **149** (5.95 g, 25 mmol) gave isoquinolinone **151** (2.91 g, 52 %) as a white solid.

Method B: Isoquinolinone **148** (1.35 g, 5 mmol) in 2M NaOH (20 mL) and EtOAc (20 mL) was heated at 50 °C for 2 hrs. After cooling to r.t. the phases were separated and the aqueous fraction extracted with EtOAc (3 x 20 mL). The combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo* to give the isoquinolinone **151** (1.03 g, 92 %) as a white solid.

R_f [EtOAc] 0.46; **Mp** 181-183 °C (from EtOAc); lit.,[235] 181 °C (from MeOH); **IR** ν_{max} (KBr disc) 3481 (NH or OH), 3328 (NH or OH), 3005, 2936, 2853 (C-H), 1649 (C=O and Ph), 1617, 1578, 1441 (Ph), 1301, 1127, 1016 (C-O) and 824; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 7.26 (1H, s, OH), 6.26 (1H, s, C(5)H), 6.02 (1H, broad s, NH), 3.89 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.54 (2H, td, *J* 6.5 and 2.5 Hz, C(3)H_2) and 2.92 (2H, t, *J* 6.5 Hz, C(4)H_2); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 170.4− (C1=O), 156.9− (C6 or C7), 155.9− (C8), 135.9− (C6 or C7), 135.2− (C8a), 105.8− (C4a), 101.8+ (C5), 60.7+ (OCH_3), 56.0+ (OCH_3), 40.3− (C3) and 28.1− (C4); **MS** (+ESI) *m/z* 246 ($M+Na^+$, 100 %) and 469 ($2M+Na^+$, 44); **HRMS** (+ESI) Found $M+Na^+$, 246.0724; $C_{11}H_{13}NO_4Na$ requires $M+Na^+$ 246.0742; **HPLC** t_R 10.4 (100 %).

2,3,4,9-Tetrahydro-β-carbolin-1-one (153)



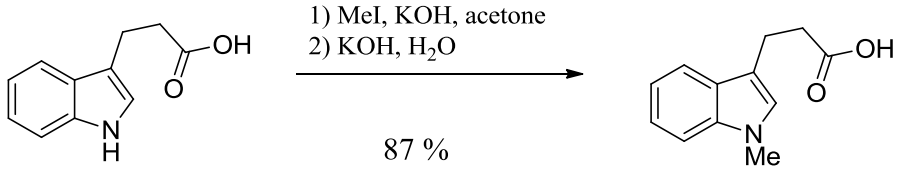
152 **153**

Following general procedure 1A, propionic acid **152** (945 mg, 5 mmol) gave carbolinone **153** (684 mg, 74 %); following general procedure 1B, **152** (567 mg, 3 mmol) gave **153** (374 mg, 67 %); and following general procedure 1C, **152** (945 mg, 5 mmol) gave **153** (806 mg, 87 %) as a white solid.

R_f [EtOAc] 0.39; **Mp** 186-188 °C (from EtOAc); lit.,[236] 183-185 °C; **IR** ν_{max}(KBr disc) 3212 (NH), 2935, 2871 (CH), 1664 (C=O), 1545, 1512, 1489, 1459, 1416 (Ph and CH), 1327 and 1291 (CO and CN); **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 10.45 (1H, s, N(9)H), 7.58 (1H, d, *J* 7.5 Hz, C(5)H), 7.51 (1H, d, *J* 7.5 Hz, C(8)H), 7.29 (1H, ddd, *J* 7.5, 7.5 and 1.0 Hz, C(7)H), 7.13 (1H, ddd, *J* 7.5, 7.5 and 1.0 Hz, C(6)H), 6.77 (1H, broad s, N(2)H), 3.72 (2H, t, *J* 7.0 Hz, C(3)H_2) and 3.06 (2H, t, *J* 7.0 Hz, C(4)H_2); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 163.7− (C1=O), 137.6− (C8a), 126.1− (C9a), 125.2+ (C7), 125.1− (C4b), 120.2+ (C5), 120.2+ (C6), 120.1− (C4a) 112.7+ (C8), 42.1− (C3) and 20.8− (C4); **MS** (+ESI) *m/z* 209 ($M+Na^+$, 61 %) and 395 ($2M+Na^+$, 100); **HRMS** (+ESI) Found $M+Na^+$, 209.0681; $C_{11}H_{10}N_2ONa$ requires $M+Na^+$ 209.0691; **HPLC** t_R 11.7 (97 %).

Spectroscopic data is consistent with that reported by Luis *et al.*[237] and Hamann *et al.*[238]

3-(1'-Methyl-1*H*-indol-3'-yl)-propionic acid (159)



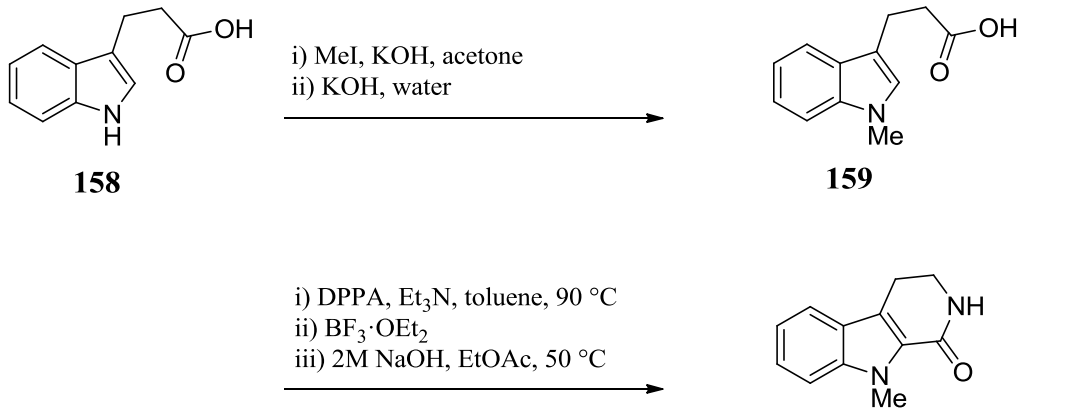
158 **159**

Following the procedure reported by Compernolle,[104] MeI (1.56 mL, 25 mmol) was added to a rapidly stirred mixture of 3-indolepropionic acid **158** (946 mg, 5 mmol) and KOH (1.7 g, 30 mmol), in acetone (50 mL). After 16 hrs at r.t. the solvent was removed *in vacuo.* The residue was dissolved in H_2O (100 mL), KOH (1.4 g, 25 mmol) added and the solution stirred at reflux for 2.5 hrs. On cooling and acidifying to pH 2 with 6M HCl, the solid was filtered off, washed with H_2O and dried to give product **159** (889 mg, 87 %) as a white solid without further purification

IR ν_{max}(KBr disc) 3446 (OH), 3055, 2912, 2705, 2611 (CH), 1710 (C=O), 1473, 1424 (Ph), 1325, 1291 (CO) and 735 (CH); **^{1}H NMR** δ_H(400 MHz, $CDCl_3$)

7.94 (1H, broad s, CO_2H), 7.58 (1H, d, *J* 7.5 Hz, C(7')H), 7.28 (1H, d, *J* 7.0 Hz, C(4')H), 7.22 (1H, ddd, *J* 7.5, 7.5 and 1.1 Hz, C(6')H), 7.10 (1H, ddd, *J* 7.0, 7.0 and 1.0 Hz, C(5')H), 6.87 (1H, s, C(2')H), 3.73 (3H, s, NCH_3), 3.10 (2H, t, *J* 7.5 Hz, C(3)H_2) and 2.76 (2H, t, *J* 7.5 Hz, C(2)H_2); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 178.5− (CO_2H), 127.5− (C3'), 126.3+ (C2'), 122.1− (C3a' or C7a'), 121.6+ (C6'), 118.8+ (C5' or C7'), 118.7+ (C5' or C7'), 113.1− (C3a' or C7a'), 109.2+ (C4'), 34.7− (C3), 32.6+ (NCH_3) and 20.3− (C2); **MS** (+ESI) *m/z* 204 ($M+H^+$, 88 %) and 226 ($M+Na^+$, 100); **HRMS** (+ESI) Found $M+Na^+$, 226.0831; $C_{12}H_{13}NO_2Na$ requires $M+Na^+$ 226.0844.

9-Methyl-2,3,4,9-tetrahydro-β-carbolin-1-one (160)



Method A: Following the procedure reported by Compernolle,[104] MeI (1.8 mL, 28 mmol) was added to a vigorously stirred mixture of KOH (1.9 g, 34 mmol) and 3-indolepropionic acid **158** (1.08 mg, 5.7 mmol) in acetone (60 mL). After 72 hrs at r.t. the solvent was removed under reduced pressure. The residue was suspended in H_2O (120 mL), KOH (1.6 g, 28 mmol) was added and the solution stirred at reflux for 2 hrs. After cooling to 0 °C, the solution was acidified to pH 2 with 6M HCl and extracted with EtOAc (3 x 50 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, filtered and the solvent removed *in vacuo* to yield the crude intermediate acid **159** as a white solid.

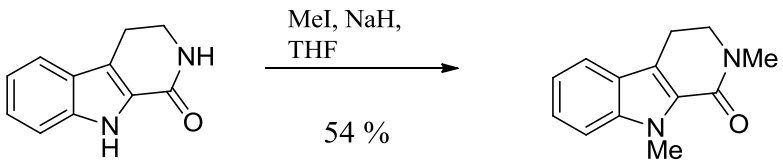
Following the general procedure 1C, the crude carboxylic acid gave the lactam **160** (0.994 g, 87 %) as a white solid.

Method B: Following general procedure 1B, acid **159** (812 mg, 4 mmol) gave carbolinone **160** (385 mg, 45 %).

Method C: MeI (311 µL, 5 mmol) was added to a vigorously stirred mixture of carbolinone **153** (180 mg, 0.697 mmol) and KOH (336 mg, 6 mmol) in acetone (10 mL) as r.t.. After 5 hrs, the reaction was quenched with 2M HCl (12 mL) and extracted with EtOAc (3 x 15 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. Column chromatography [silica, PE-EtOAc gradient from 50:50 to 40:60] afforded gave the carbolinone **160** (134 mg, 69 %) as a white solid.

R_f [PE-EtOAc 3:7] 0.37; **Mp** 160-162 °C (from EtOAc); lit.,[236] 157-158 °C; **IR** ν_{max}(KBr disc) 3312 (NH), 2934, 2869 (CH), 1656 (C=O), 1489, 1467 (Ph), 1289 (CN) and 732 (CH); **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 7.59 (1H, d, *J* 8.0 Hz, C(5)H), 7.38-7.33 (2H, m C(8)H and C(6)H), 7.15 (1H, dd, *J* 8.0 and 8.0 Hz, C(7)H), 5.70 (1H, broad s, N(2)H), 4.11 (3H, s, N(9)CH_3), 3.65 (2H, td, *J* 7.0 and 2.5 Hz, C3) and 3.05 (2H, t, *J* 7.0 Hz, C4); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 163.3− (C=O), 139.0− (C8a), 125.8− (C9a), 124.9+ (C7), 124.1− (C4b), 120.3+ (C5), 120.0+ (C6), 119.8− (C4a), 110.2+ (C8), 41.9− (C3), 31.2+ (NCH_3) and 21.1− (C4); **MS** (+ESI) 201 ($M+H^+$, 62 %) and 223 ($M+Na^+$, 100); **HRMS** (+ESI) Found $M+Na^+$, 223.0839; $C_{12}H_{12}N_2ONa$ requires $M+Na^+$ 223.0847; **HPLC** t_R 12.1 (99 %).

2,9-Dimethyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-one (161)



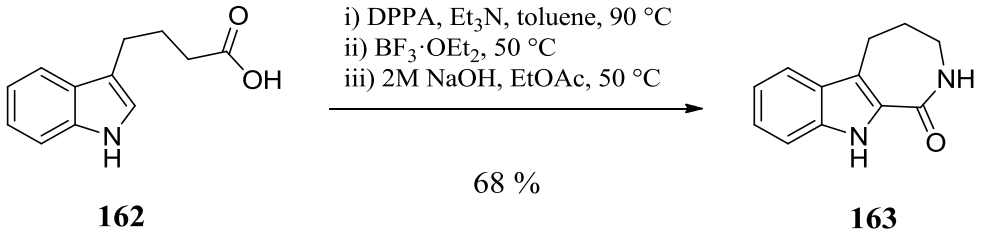
153 **161**

NaH (60 % dispersion in mineral oil) (100 mg, 2.5 mmol) was added to a vigorously stirred suspension of lactam **153** (180 mg, 0.97 mmol) in THF (3 mL) at 0 °C under Ar. After 30 mins, MeI (155 µL, 2.5 mmol) was added and the reaction

stirred at r.t. for 18 hrs. The reaction was quenched with saturated aqueous NH_4Cl (15 mL) and extracted with EtOAc (3 x 15 mL). The organic fractions were combined, washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo*. Column chromatography [silica, PE-EtOAc gradient from 70:30 to 50:50] afforded the dimethylcarbolinone **161** (113 mg, 54 %) as a cream solid.

Mp 66-69 °C (Et_2O); lit.,[236] 65-66 °C; **IR** ν_{max}(Thin film) 2934, 1647 (C=O), 1545, 1497, 1468, 1323, 1251, 1235 and 1074; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 7.49 (1H, d, *J* 8.0 Hz, C(5)H), 7.29 (1H, d, *J* 8.0 Hz, C(8)H), 7.24 (1H, ddd, *J* 8.5, 7.5 and 1.0 Hz, C(7)H), 7.06 (1H, ddd, *J* 8.0, 6.5 and 1.5 Hz, C(6)H), 4.04 (3H, s, N(9)CH_3), 3.58 (2H, t, *J* 7.0 Hz, C(3)H_2), 3.05 (3H, s, N(2)CH_3) and 2.97 (2H, t, *J* 7.0 Hz, C(4)H_2); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 162.1− (C1=O), 139.0− (C8a), 126.4− (C9a), 124.4+ (C7), 124.0− (C4b), 120.0+ (C5), 119.9+ (C6), 118.2− (C4a), 110.1+ (C8), 49.9− (C3), 34.1+ (N(2)CH_3), 31.17+ (N(9)CH_3) and 20.6− (C4); **MS** (+ESI) *m/z* 215 ($M+H^+$, 100 %) and 237 ($M+Na^+$, 9); **HRMS** (+ESI) Found $M+Na^+$, 237.0956; $C_{13}H_{14}N_2ONa$ requires $M+Na^+$ 237.0998; **HPLC** t_R 15.7 (92 %).

3,4,5,10-Tetrahydro-2*H*-azepino[3,4-*b*]indol-1-one (163)



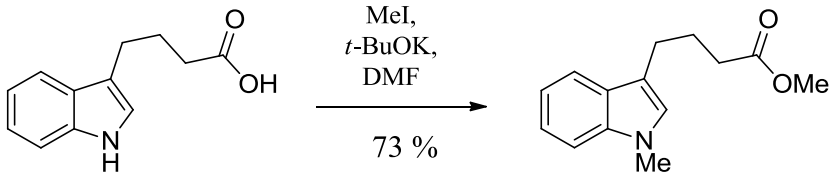
162 **163**

Following general procedure 1B, butyric acid **162** (1.02 g, 5 mmol) gave azepinone **163** (140 mg, 14 %). Following general procedure 1C, performing the cyclisation step at r.t., butyric acid **162** (1.02 g, 5 mmol) gave the lactam **163** (406 mg, 40 %); performing the cyclisation step at 50 °C **162** (1.02 g, 5 mmol) gave azepinone **163** (686 mg, 68 %) and performing the cyclisation at 80 °C **162** (395 mg, 1.94 mmol) gave **163** (351 mg, 90 %) as a white solid.

R_f [EtOAc] 0.42; **Mp**: 227-230 °C (from EtOAc); lit.,[239] 220 °C (from acetone); **IR** ν_{max}(KBr disc) 3268 (NH), 2940, 2865 (CH), 1628 (C=O), 1545, 1481, 1410 (Ph and CH), 1332 and 1296 (CO and CN); **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 9.30 (1H, broad s, N(10)H), 7.60 (1H, d, *J* 8.0 Hz, C(6)H), 7.41 (1H, d, *J* 8.0 Hz, C(9)H), 7.31 (1H, ddd, *J* 8.0, 7.0 and 1.0 Hz, C(8)H), 7.13 (1H, ddd, *J* 8.0, 7.0 and 1.0 Hz, C(7)H), 6.53 (1 H, broad s, N(2)H), 3.50 (1 H, t, *J* 5.0 Hz, C(3)H_AH_B), 3.49 (1 H, t, *J* 5.0 Hz, C(3)H_AH_B), 3.15 (2H, t, *J* 6.5 Hz, C(5)H_2) and 2.23-2.17 (2 H, m, C(4)H_2); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 165.5− (C1=O), 135.8− (C9a), 128.0− (C5b), 126.5− (C10a), 125.2+ (C8), 120.3+ (C6), 119.8+ (C7), 119.0− (C5a), 111.8+ (C9), 43.0− (C3), 26.7− (C4) and 25.8− (C5); **MS** (+ESI) *m/z* 201 ($M+H^+$, 10 %), 223 ($M+Na^+$, 29) and 423 ($2M+Na^+$, 100); **HRMS** (+ESI) Found $M+Na^+$, 223.0848; $C_{12}H_{12}N_2ONa$ requires $M+Na^+$ 223.0847; **HPLC** t_R 13.0 (100 %).

Spectroscopic data is consistent with that reported by Thakur *et al.*[240]

Methyl 4-(1'-Methyl-1H-indol-3'-yl)-butanoate (164)

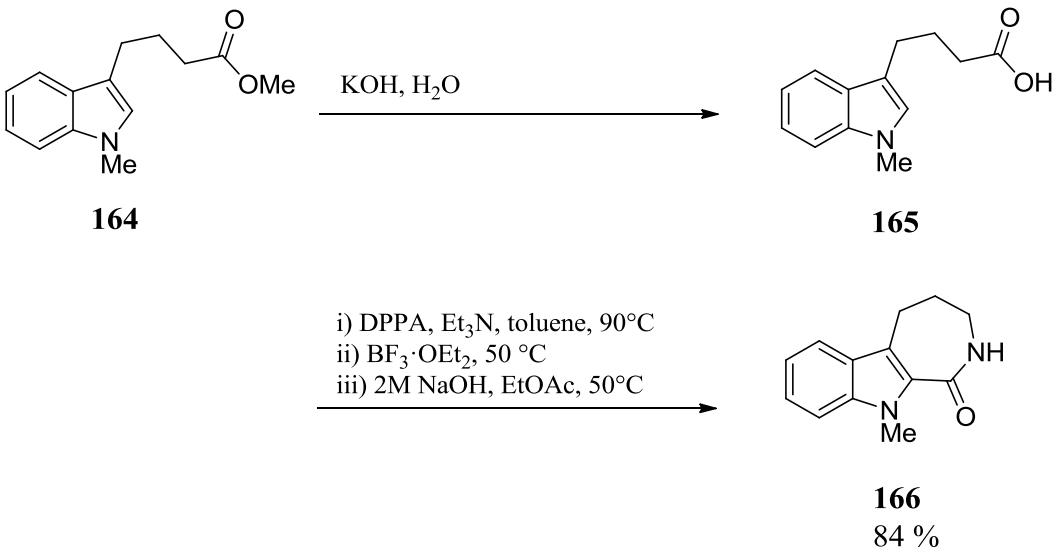


162 **164**

Following the procedure reported by Perregaard,[108] *t*-BuOK (2.52 g, 22.5 mmol) was added portionwise over 5 min to a stirred solution of indole-3-butyric acid **162** (1.52 g, 7.5 mmol) in anhydrous DMF (15 mL) under N_2. The mixture was cooled to 0 °C and MeI (3.73 mL, 60 mmol) added slowly over 10 min. The reaction was allowed to warm to r.t. and stirred for 16 h. H_2O (65 mL) was added, the layers separated and the aqueous fraction extracted with EtOAc (4 x 20 mL). The organic fractions were combined, washed with brine, dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo*. After column chromatography [silica, PE−EtOAc gradient from 100:0 to 0:100] the *N*-methyl ester **164** (1.27 g, 73%) was isolated as an oil.

R_f [PE-EtOAc, 70:30] 0.51; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 7.62 (1H, dd, *J* 8.0 and 1.0 Hz, C(7')H), 7.31 (1H, dd, *J* 8.0 and 1.0 Hz, C(4')H), 7.25 (1H, ddd, *J* 8.0, 8.0 and 1.0 Hz, C(6')H), 7.13 (1H, ddd, *J* 8.0, 8.0 and 1.0 Hz, C(5')H), 6.86 (1H, s, C(2')H), 3.76 (3H, s, NCH_3), 3.69 (3H, s, OCH_3), 2.83 (2H, t, *J* 7.5 Hz, C(4)H_2), 2.42 (2H, t, *J* 7.5 Hz, C(2)H_2) and 2.11-2.03 (2H, m, C(3)H_2); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 174.1− (CO_2H), 137.0− (C7a'), 127.8− (C3a'), 126.3+ (C2'), 121.4+ (C6'), 118.9+ (C7'), 118.6+ (C5'), 114.0− (C3'), 109.1+ (C4'), 51.4+ (OCH_3), 33.6− (C2), 32.5+ (NCH_3), 25.5− (C3) and 24.3− (C4); **MS** (+ESI) *m/z* 254 ($M+Na^+$, 100 %); **HRMS** (+ESI) Found $M+Na^+$, 254.1144; $C_{14}H_{17}NO_2Na$ requires $M+Na^+$ 254.1157.

10-Methyl-2,3,4,5-tetrahydroazepino[3,4-b]indol-1(10H)-one (166)



164 **165** **166**
84 %

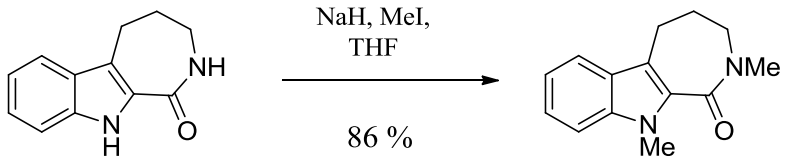
KOH (1.55 g, 28 mmol) was added to a rapidly stirred suspension of the ester **164** (1.28 g, 5.6 mmol) in H_2O (100 mL) at r.t. and the reaction heated at reflux for 4 hrs. After cooling to 0 °C the solution was acidified to pH 2 with 6M HCl and extracted with EtOAc (3 x 30 mL). The combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo* to afford the acid intermediate acid **165** as a white solid.

Following general procedure 1C, performing the $BF_3{\cdot}OEt_2$ mediated cyclisation at r.t., the crude acid intermediate gave the azepinone **166** (3.9 mmol

scale, 301 mg, 36%) and performing the cyclisation at 50 °C gave **166** (5.56 mmol scale, 1.008 g, 85%) as a white solid.

R_f [PE-EtOAc 7:3] 0.15; **Mp** 131-134 °C (from EtOAc); **IR** ν_{max} (KBr disc) 3467 (NH), 3277, 3139, 3055, 2931 (CH), 1658 (C=O), 1535, 1475, 1434 (Ar), 1318 (CN) and 735 (CH); **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 7.62 (1H, d, *J* 8.0 Hz, C(6)H), 7.37 (1H, dd, *J* 8.0 and 1.0 Hz, C(9)H), 7.34 (1H, ddd, *J* 8.5, 8.0 and 1.0 Hz, C(8)H), 7.15 (1H, ddd, *J* 8.0, 6.0 and 2.0 Hz, C(7)H), 6.53 (1H, broad s, N(2)H), 4.00 (3H, s, N(10)CH_3), 3.35 (1H, t, *J* 6.0 Hz, C(3)H_AH_B), 3.34 (1H, t, *J* 6.0Hz, C(3)H_AH_B), 3.12 (2H, t, *J* 7.0 Hz, C(5)H_2) and 2.17-2.11 (2H, m, C(4)H_2); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 167.2− (C1=O), 138.7− (C9a), 127.8− (C10a), 126.2− (C5b), 124.6+ (C8), 119.8+ (C6), 119.6+ (C7), 118.9− (C5a), 110.0+ (C9), 41.4− (C3), 31.8+ (NCH_3), 29.0− (C4) and 22.3− (C5); **MS** (+ESI) *m/z* 237 ($M+Na^+$, 69 %) and 451 ($2M+Na^+$, 100); **HRMS** (+ESI) Found $M+Na^+$, 237.1001; $C_{13}H_{14}N_2ONa$ requires $M+Na^+$ 237.1004; **HPLC** t_R 14.3 (100 %).

2,10-Dimethyl-2,3,4,5-tetrahydroazepino[3,4-b]indol-1(10H)-one (167)



163 **167**

NaH (60 % dispersion in mineral oil) (120 mg, 3 mmol) was added to a vigorously stirred suspension of lactam **163** (187 mg, 0.935 mmol) in THF (5 mL) at 0 °C under Ar. After 30 mins, MeI (185 μL, 3 mmol) was added and the reaction stirred at r.t. for 16 hrs, then quenched with saturated aqueous NH_4Cl (15mL) and extracted with EtOAc (3 x 15 mL). The organic fractions were combined, washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo*. After column chromatography [silica, light PE-EtOAc gradient from 100:0 to 50:50] azepinone **167** (183 mg, 86 %) was isolated as a white solid.

Mp 106-110 °C (Et_2O); lit.,[241] 104-106 °C (PE 60-80 °C); **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 7.60 (1H, ddd *J* 8.0, 1.0 and 1.0 Hz, C(6)H), 7.35 (1H, ddd, *J* 8.0, 1.0 and 1.0 Hz, C(9)H), 7.31 (1H, ddd, *J* 8.0, 6.5 and 1.0 Hz, C(8)H), 7.13 (1H, ddd, *J* 8.0, 6.5 and 1.0 Hz, C(7)H), 3.96 (3H, s, N(2)CH_3), 3.45 (2H, dd, *J* 6.0 and 6.0 Hz, C(3)H_2), 3.20 (3H, s, N(10)CH_3), 3.02 (2H, dd, *J* 6.0 and 6.0 Hz, C(5)H_2) and 2.20-2.13 (2H, m, C(4)H_2); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 165.3− (C1=O), 138.4− (C9a), 129.5− (C10a), 126.0− (C5b), 124.1+ (C8), 119.5+ (C6 or C7), 119.5+ (C6 or C7), 117.2− (C5a), 109.9+ (C9), 49.6− (C3), 34.9+ (N(2)CH_3), 31.5+ (N(10)CH_3), 28.0− (C4) and 20.7− (C5); **MS** (+ESI) *m/z* 229 ($M+H^+$, 100 %) and 251 ($M+Na^+$, 25); **HRMS** (+ESI) Found $M+Na^+$, 251.1171; $C_{14}H_{16}N_2ONa$ requires $M+Na^+$ 251.1160; **HPLC** t_R 13.5 (100 %).

5.2.2. Synthesis of AB-ring Analogues by Dehydrogenation of Lactams

General Procedure 2: Dehydrogenation of lactam rings

Method A: Dichlorodicyanoquinoline (452 mg, 4 mmol) was added to a stirred solution of lactam (0.5 mmol) in dioxane (10 mL) at r.t. under N_2, then the reaction heated at 110 °C for between 1 and 24 hrs. After cooling, the solvent was removed and the residue stirred in 2M NaOH (10 mL) for 30 mins then extracted with EtOAc (4 x 10 mL). The combined organic fractions were washed with H_2O (2 x 10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo*. After column chromatography [silica, MeOH-CH_2Cl_2 gradient from 0:100 to 5:95] the product was isolated.

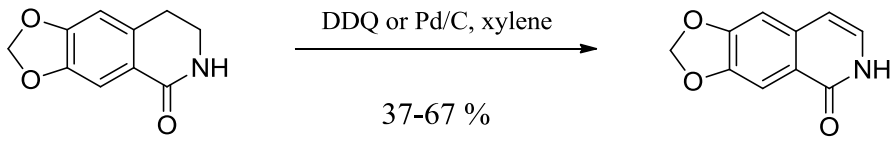
Method B: 10 % Palladium on activated carbon (7 mol%) was added to a vigorously stirred, degassed solution of lactam in anhydrous xylene (8 mL/mmol) under N_2, then the reaction was heated at reflux for 24 hrs. The catalyst was removed by filtration through celite and washed with hot MeOH, then the solvent was removed *in vacuo*. The product was recrystallised from EtOAc, without need for column chromatography.

Method C: 10 % Palladium on activated carbon (15 mol%) was added to a vigorously stirred, degassed solution of lactam in anhydrous xylene (8 mL/mmol) under N_2, then the reaction was heated at reflux for 24 hrs. After cooling to r.t., the

mixture was diluted with MeOH, SiO_2 added and then heated at reflux for 30 mins. The solvent was removed *in vacuo* and column chromatography [silica, MeOH-CH_2Cl_2 gradient from 0:100 to 5:95] afforded the product.

Method D: A degassed suspension lactam and 10 % palladium on activated carbon (10 mol %) in xylene (5 mL/ mmol) was heated in the microwave at 200 °C for 30-60 mins. The mixture was diluted with MeOH, SiO_2 added and then heated at reflux for 30 mins. The solvent was removed *in vacuo* and column chromatography [silica, MeOH-CH_2Cl_2 gradient from 0:100 to 5:95] afforded the product.

6*H*-1,3-Dioxolo[4,5-*g*]isoquinolin-5-one (172)



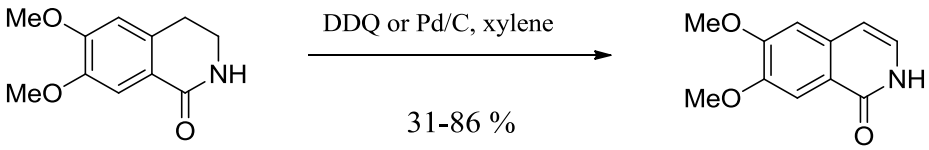
144 **172**

Following general procedure 2A dihydroisoquinolinone **144** (96 mg, 0.5 mmol) gave isoquinolinone **172** (35 mg, 37 %); following general procedure 2B **144** (199 mg, 1.04 mmol) gave **172** (106 mg, 54 %); following procedure 2B using 33 mol% Pd/C **144** (1.53 g, 8 mmol) gave **172** (637 mg, 42 %); and following procedure 2C **144** (192g, 1 mmol) gave **172** (127 mg, 67 %) as a white solid.

Mp sublimes above 185 °C, then recrystallises and melts 281-284 °C with accompanying decomposition (from EtOAc); **IR** ν_{max}(KBr disc) 2907, 2847, 1654 (C=O), 1582, 1498, 1479, 1460, 1254 and 1036; **^{1}H NMR** δ_H(400 MHz, d_6-DMSO) 11.14 (1H, broad s, NH), 7.49 (1H, s, C(8)H), 7.14 (1H, s, C(5)H), 7.05 (1 H, dd, *J* 7.0 and 5.5 Hz, C(3)H), 6.44 (1H, d, *J* 7.0 Hz, C(4)H) and 6.15 (2H, s, OCH_2O); **^{13}C NMR** δ_C(100 MHz, d_6-DMSO) 161.1− (C1=O), 151.4− (C7-O), 147.1− (C6-O), 135.1− (C4a or C8a), 127.5+ (C3), 121.3− (C4a or C8a), 104.7+ (C4), 104.0+ (C8), 103.9+ (C5) and 101.8− (CH_2); **MS** (+ESI) *m/z* 212 ($M+Na^+$, 85 %) and 401 ($2M+Na^+$, 100); **HRMS** (+ESI) (Found $M+Na^+$, 212.0316; $C_{10}H_7NO_3Na$ requires $M+Na^+$ 212.0324; **HPLC** t_R 9.5 (100 %).

Spectroscopic data is consistent with that reported by Xie *et al.* [242]

6,7-Dimethoxyisoquinolin-1(2H)-one (173)



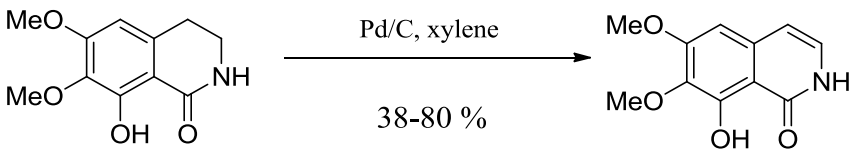
147 **173**

Following general procedure 2A, dihydroisoquinolinone **147** (104 mg, 0.5 mmol) gave isoquinolinone **173** (32 mg, 31 %); following general procedure 2B **147** (207 mg, 1 mmol) gave **173** (126 mg, 61 %); and following general procedure 2C **147** (207 mg, 1 mmol) gave **173** (178 mg, 86 %) as a white solid.

Mp sublimes above 205 °C then recrystallises and melts at 244-246 °C (EtOAc), lit.,[243] 244-245 °C (from $CHCl_3$-PhH); **IR** ν_{max}(KBr disc) 2923, 2853, 1639 (C=O), 1607, 1505, 1470 and 1273; **^{1}H NMR** δ_H(400 MHz, CD_3OD) 7.70 (1H, s, C(8)H), 7.13 (1H, s, C(5)H), 7.09 (1 H, d, *J* 7.0 Hz, C(3)H), 6.34 (1H, d, *J* 7.0 Hz, C(4)H), 3.96 (3H, s, C(7)OCH_3) and 3.94 (3H, s, C(6)OCH_3); **^{13}C NMR** δ_C(100 MHz, CD_3OD) 164.3− (C=O), 155.6− (C7-O), 150.9− (C6-O), 135.8− (C8a), 127.3+ (C3), 120.7− (C4a), 107.8+ (C4, C5 or C8), 107.7+ (C4, C5 or C8), 107.7+ (C4, C5 or C8), 56.5+ (OCH_3) and 56.4+ (OCH_3); **MS** (+ESI) *m/z* 206 ($M+H^+$, 35 %), 228 ($M+Na^+$, 17) and 433 ($2M+Na^+$, 100); **HRMS** (+ESI) Found $M+H^+$, 206.796; $C_{11}H_{12}NO_3$ requires $M+H^+$ 206.0817; **HPLC** t_R 8.8 (100 %).

Spectroscopic data is consistent with that reported by Sakamoto *et al.*[244]

8-Hydroxy-6,7-dimethoxy-1-oxoquinoline (174)

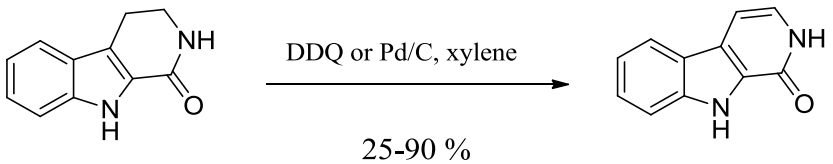


151 **174**

Following general procedure 2B, dihydroisoquinolinone **151** (123 mg, 0.55 mmol) gave isoquinolinone **174** (62 mg, 51 %); following general procedure 2B using 33 mol% Pd/C **151** (1.31 g, 5.95 mmol) gave **174** (644 mg, 49 %); following general procedure 2C **151** (223 mg, 1 mmol) gave **174** (85 mg, 38 %); and following general procedure 2D **151** (112 mg, 0.5 mmol) gave **174** (88 mg, 80 %) as a white solid.

Mp sublimes above 210 °C then recrystallises, melts at 244-247 °C (from EtOAc); **IR** ν_{max}(KBr disc) 3329 (OH), 2936, 2853 (CH), 1648, 1618, 1578, 1440, 1382, 1303 (C-O), 1235, 1127, 1017 and 824; **^{1}H NMR** δ_H(400 MHz, d_6-DMSO) 13.26 (1H, s, OH), 11.53 (1H, s, NH), 7.11 (1H, d, *J* 7.0 Hz, C(3)H), 6.73 (1H, s, C(5)H), 6.56 (1H, d, *J* 7.5 Hz, C(4)H), 3.87 (3H, s, OCH_3) and 3.72 (3H, s, OCH_3); **^{13}C NMR** δ_C(100 MHz, d_6-DMSO) 165.7− (C1=O), 157.8− (C7), 153.7− (C8), 135.1− (C8a), 132.8− (C6), 127.8+ (C3), 106.9− (C4a), 106.7+ (C4), 97.9+ (C5), 59.8+ (OCH_3) and 55.8+ (OCH_3); **MS** (+ESI) *m/z* 222 ($M+H^+$, 100 %) and 244 ($M+Na^+$, 56); **HRMS** (+ESI) Found $M+Na^+$, 244.0619; $C_{11}H_{11}NO_4Na$ requires $M+Na^+$ 244.0580; **HPLC** t_R 10.6 (96 %).

2,9-Dihydro-1H-pyrido[3,4-b]indol-1-one (175)



153 **175**

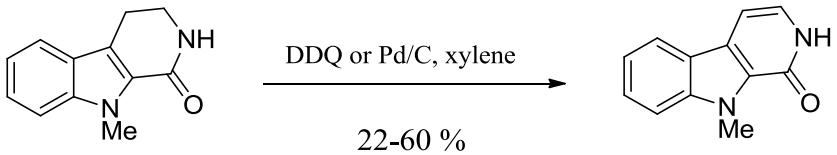
Following general procedure 2A carbolinone **153** (93 mg, 0.5 mmol) gave carbolinone **175** (23 mg, 25 %); following general procedure 2A using 3 mmol DDQ, carbolinone **153** (93 mg, 0.5 mmol) gave carbolinone **175** (53 mg, 58 %); following general procedure 2B **153** (186 mg, 1 mmol) gave **175** (72 mg, 39 %); and following procedure 2D **153** (558 mg, 3 mmol) gave **175** (497 mg, 90 %) as a white solid.

R_f [CH_2Cl_2-MeOH 95:5] 0.28; **Mp** sublimes above 236 °C (from EtOAc); lit.,[245] 259 °C (from PhH); **IR** ν_{max}(Thin film) 2918, 1651 (C=O), 1614, 1424, 1327

and 725; **^{1}H NMR** δ_H(400 MHz, d_6-DMSO) 11.90 (1H, s, N(9)H), 11.35 (1H, s, N(2)H), 8.00 (1H, d, *J* 8.0 Hz, C(5)H), 7.49 (1H, d, *J* 8.0 Hz, C(8)H), 7.38 (1H, ddd, *J* 8.0, 7.0 and 1.0 Hz, C(7)H), 7.15 (1H, ddd *J* 8.0, 7.0 and 1.0 Hz, C(6)H), 7.07-7.04 (1H, m, C(3)H) and 6.96 (1H, d, *J* 7.0 Hz, C(4)H); **^{13}C NMR** δ_C(100 MHz, d_6-DMSO) 155.7− (C=O), 139.0− (C8a), 128.0− (C4a), 126.2+ (C7), 124.5+ (C3), 124.2− (C9a), 122.0− (C4b), 121.3+ (C5), 119.4+ (C6), 112.4+ (C8) and 99.7+ (C4); **MS** (+ESI) *m/z* 185 ($M+H^+$, 100 %), 207 ($M+Na^+$, 20) and 391 ($2M+Na^+$, 76); **HRMS** (+ESI) Found $M+H^+$, 185.0710; $C_{11}H_9N_2O$ requires $M+H^+$ 185.0715; **HPLC** t_R 10.0 (100 %).

Spectroscopic data is consistent with that reported by Tahri *et al.*[246]

9-Methyl-2,9-dihydro-1H-pyrido[3,4-b]indol-1-one (176)

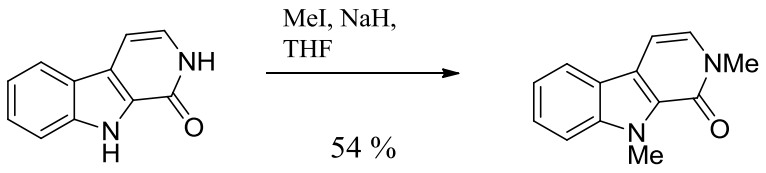


160 **176**

Following general procedure 2A carbolinone **160** (100 mg, 0.5 mmol) gave carbolinone **176** (22 mg, 22 %); and following general procedure 2B **160** (200 mg, 1 mmol) after 6 days gave **176** (119 mg, 60 %) as a white solid.

Mp 161-164 °C (from EtOAc); lit.,[247] 242-242.5 °C (from EtOH); **IR** ν_{max}(KBr disc) 3116 (NH), 2881, 2836 (CH), 1656 (C=O) 1464, 1351, 1327, 1279, 1215 and 949; **^{1}H NMR** δ_H(400 MHz, d_6-DMSO) 11.4 (1H, s, N(2)H), 8.06 (1H, d, *J* 8.0 Hz, C(5)H), 7.62 (1H, d, *J* 8.5 Hz, C(8)H), 7.50 (1H, ddd, *J* 8.0, 7.0 and 1.0 Hz C(7)H), 7.23 (1H, ddd, *J* 8.0, 7.0 and 1.0 Hz, C(6)H), 7.07 (1H, dd, *J* 7.0, 7.0 Hz, C(3)H), 6.99 (1H, d, *J* 6.0 Hz, C(4)H) and 7.23 (3H, s, N(9)CH_3); **^{13}C NMR** δ_C(100 MHz, d_6-DMSO) 156.4− (C1=O), 140.2− (C8a), 127.0− (C9a), 126.5+ (C7), 124.9+ (C3), 124.6− (C4a), 121.4+ (C5), 121.1− (C4b), 119.8+ (C6), 110.4+ (C8), 99.6+ (C4) and 31.0+ (N(9)CH_3); **MS** (+ESI) *m/z* 199 ($M+H^+$, 100 %), 221 ($M+Na^+$, 40) and 419 ($2M+Na^+$, 75); **HRMS** (+ESI) Found $M+Na^+$, 221.0675; $C_{12}H_{10}N_2ONa$ requires $M+Na^+$ 221.0691; **HPLC** t_R 14.8 (100 %).

2,9-Dimethyl-2,9-dihydro-1H-pyrido[3,4-b]indol-1-one (177)



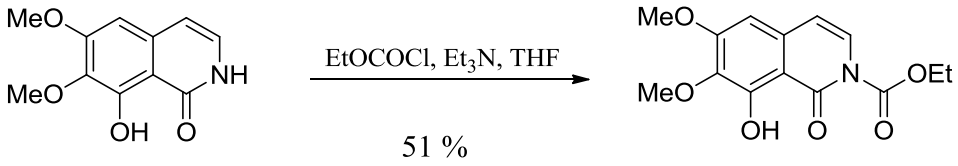
175 **177**

NaH (60 % dispersion in mineral oil) (100 mg, 2.5 mmol) was added to a vigorously stirred suspension of lactam **175** (144 mg, 0.78 mmol) in THF (3 mL) at 0 °C under Ar. After 30 mins, MeI (155 μL, 2.5 mmol) was added and the reaction stirred at r.t. for 18 hrs. The reaction was quenched with saturated aqueous NH_4Cl (15mL) and extracted with EtOAc (3 x 15 mL). The organic fractions were combined, washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo*. After column chromatography [silica, PE-EtOAc gradient from 100:0 to 50:50] the carbolinone **177** (90 mg, 54 %) was isolated as a yellow solid.

Mp 164-166 °C (from Et_2O); lit.,[247] 158.5-159 °C (from EtOH); **IR** ν_{max}(Thin film) 309, 2926, 1648 (C=O), 1589, 1531, 1473, 1331 and 1268; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 7.84 (1H, d, *J* 8.0 Hz, C(8)H), 7.42 (1H, ddd, *J* 8.0, 7.0 and 1.0 Hz, C(7)H), 7.36 (1H, d, *J* 8.0 Hz, C(5)H), 7.16 (1H, ddd, *J* 8.0, 8.0 and 2.0 Hz, C(6)H), 6.97 (1H, d, *J* 7.0 Hz, C(3)H), 6.79 (1H, d, *J* 7.0 Hz, C(4)H), 4.24 (3H, s, N(9)CH_3) and 3.60 (3H, s, N(2)CH_3); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 156.8− (C1=O), 140.9− (C8a), 128.7+ (C3), 127.3− (C9a), 126.6+ (C7), 124.6− (C4a), 121.3− (C4b), 121.0+ (C8), 119.9+ (C6), 110.0+ (C5), 100.4+ (C4), 36.7+ (N(2)CH_3) and 31.5+ (N(9)CH_3); **MS** (+ESI) *m/z* 213 ($M+H^+$, 100 %), 235 ($M+Na^+$, 9); **HRMS** (+ESI) Found $M+Na^+$, 235.0836; $C_{13}H_{16}N_2ONa$ requires $M+Na^+$ 235.0842; **HPLC** t_R 14.8 (96 %).

5.2.3. Pro-drug Synthesis

8-Hydroxy-6,7-dimethoxy-1-oxo-1*H*-isoquinoline-2-carboxylic acid ethyl ester (178)

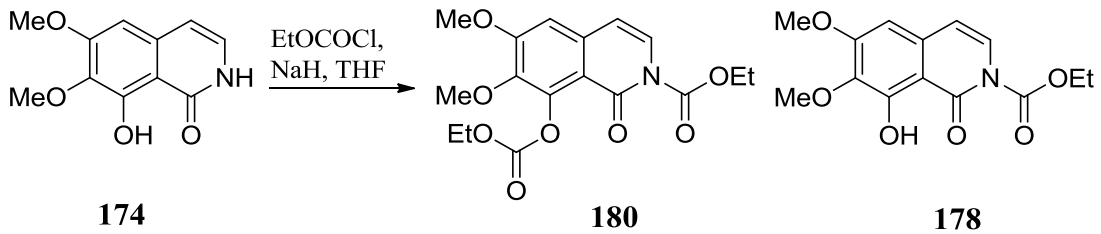


174 **178**

Ethyl chloroformate (53 µL, 0.55 mmol) was added to a stirred suspension of isoquinolinone **174** (110 mg, 0.5 mmol) and Et_3N (76 µL, 0.55 mmol) in anhydrous THF (1.5 mL) at 0 °C under N_2. The reaction was allowed to warm to r.t. and stirred for 2 hrs, then quenched with H_2O (6 mL) and extracted with EtOAc (3 x 10 mL). The combined organic fractions were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo*. After column chromatography [silica, PE-EtOAc 70:30] the carbamate product **178** (75 mg, 51 %) was isolated as a white solid.

R_f [PE-EtOAc 70:30] 0.70; **IR** ν_{max}(Thin film) 2980, 1941, 1770 (C=O), 1667 (C=O), 1594, 1559, 1505, 1411, 1300, 1246, 1199 and 1127; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 12.41 (1H, s, OH), 7.46 (1H, d, *J* 8.0 Hz, C(3)H), 6.43 (1H, s, C(5)H), 6.38 (1H, d, *J* 8.0 Hz, C(4)H), 4.52 (2H, q, *J* 7.0 Hz, OCH_2CH_3), 3.95 (3H, s, CH_3), 3.91 (3H, s, OCH_3) and 1.46 (3H, t, *J* 7.0 Hz, OCH_2CH_3); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 164.9− (C1=O), 158.9− (C6 or C7), 155.9− (C8-OH), 151.7− (CO_2Et), 135.4− (C6 or C7), 133.5− (C4a or C8a), 126.1+ (C3), 108.6+ (C4), 107.2− (C4a or C8a), 98.6+ (C5), 65.2− (OCH_2CH_3), 60.7+ (OCH_3), 56.1+ (OCH_3) and 14.1+ (OCH_2CH_3). **MS** (+ESI) *m/z* 294 ($M+H^+$, 31 %), 316 ($M+Na^+$, 17) and 609 ($2M+H^+$, 100); **HRMS** (+ESI) Found $M+H^+$, 294.0975; $C_{14}H_{16}NO_6$ requires $M+H^+$ 294.0972.

8-Ethoxycarbonyloxy-6,7-dimethoxy-1-oxo-1*H*-isoquinoline-2-carboxylic acid ethyl ester (180)

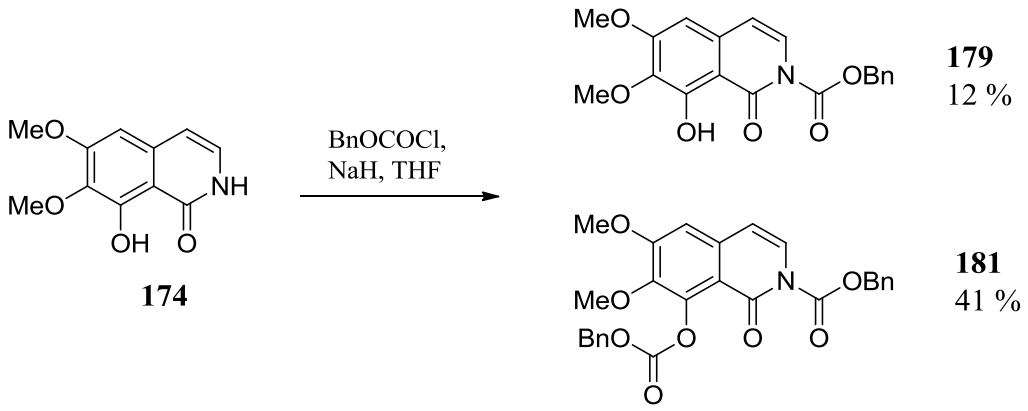


174 **180** 26 % **178** 37 %

NaH (60 % dispersion in mineral oil) (80 mg, 1.2 mmol) was added to a vigorously stirred suspension of isoquinolinone **174** (110 mg, 0.5 mmol) in anhydrous THF (3 mL) at 0 °C under N_2. After 45 mins, ethyl chloroformate (115 µL, 1.2 mmol) was added, the reaction was allowed to warm to r.t. and stirred for 3 hrs, then quenched with H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic fractions were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo*. After column chromatography [silica, PE-EtOAc 70:30] the carbonate product **180** (48 mg, 26 %) was isolated as a white solid and the carbamate **178** (54 mg, 37 %) as white a solid.

R_f [PE-EtOAc 60:40] 0.80; **IR** ν_{max}(KBr disc) 2990, 3947, 1753 (C=O), 1731 (C=O), 1685 (C=O), 1605, 1503, 1469, 1409, 1370, 1311, 1243, 1130, 1091, 1030, 1006 and 975; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 7.44 (1H, d, *J* 8.0 Hz, C(3)H), 6.73 (1H, s, C(5)H), 6.27 (1H, d, *J* 8.0 Hz, C(4)H), 4.44 (2H, q, *J* 7.0 Hz, OCH_2CH_3), 4.36 (2H, q, *J* 7.0 Hz, OCH_2CH_3), 3.94 (3H, s, OCH_3), 3.87 (3H, s, OCH_3) and 1.42-1.38 (6H, m, OCH_2CH_3); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 158.1− (C1=O), 157.8− (C6 or C7), 152.8− (NCO_2Et or OCO_2Et), 152.7− (NCO_2Et or OCO_2Et), 145.1− (C8), 141.7− (C6 or C7), 134.6− (C4a or C8a), 127.5+ (C3), 113.7− (C4a or C8a), 106.4+ (C4), 105.2+ (C5), 65.1− (OCH_2CH_3), 64.7− (OCH_2CH_3), 61.5+ (OCH_3), 56.1+ (OCH_3), 14.2+ (OCH_2CH_3) and 14.0+ (OCH_2CH_3); **MS** (+ESI) *m/z* 366 ($M+H^+$, 35 %), 388 ($M+Na^+$, 13) and 753 ($2M+Na^+$, 100); **HRMS** (+ESI) Found $M+H^+$, 366.1187; $C_{17}H_{20}NO_8$ requires $M+H^+$ 366.1183.

Benzyl 8-hydroxy-6,7-dimethoxy-1-oxoisoquinoline-2(1H)-carboxylate (179) and benzyl 8-(benzyloxycabonyloxy)-6,7-dimethoxy-1-oxoisoquinoline-2(1H)-carboxylate (181)



NaH (60 % dispersion in mineral oil) (80 mg, 2 mmol) was added to a vigorously stirred suspension of isoquinolinone **174** (110 mg, 0.5 mmol) in anhydrous THF (3 mL) at 0 °C under N_2. After 45 mins, benzyl chloroformate (171 µL, 1.2 mmol) was added. The reaction was allowed to warm to r.t. and stirred for 3 hrs, then quenched with H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic fractions were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo*. After column chromatography [silica, PE-EtOAc gradient from 100:0 to 60:40] the phenol product **179** (22 mg, 12 %) was isolated as a white solid and carbonate product **181** (100 mg, 41 %) as an oil.

Phenol (179)

R_f [PE-EtOAc 50:50] 0.4; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 12.41 (1H, s, OH) 7.49 (2H, d, *J* 7.0 Hz, Ph), 7.45 (1H, d, *J* 8.0 Hz, C(3)H), 7.43-7.37 (3H, m, Ph), 6.41 (1H, s, C(5)H), 6.36 (1H, d, *J* 8.0 Hz, C(4)H), 5.46 (2H, s, OC*H*$_2$Ph), 3.94 (3H, s, OCH_3) and 3.91 (3H, s, OCH_3); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 164.9− (C(1)=O), 158.9− (C6 or C7), 155.9− (C8), 151.6− (N*C*O_2Bn), 135.4− (C6 or C7), 134.1− (C4a or C8a), 133.4− (Ph), 128.9+ (Ph), 128.8+ (Ph), 128.5+ (Ph), 126.0+ (C3), 108.7+ (C4), 107.1− (C4a or C8a), 98.7+ (C5), 70.4− (O*C*H_2Ph), 61.7+ (OCH_3) and 56.1+ (OCH_3); **MS** (+ESI) *m/z* 356 ($M+H^+$, 100 %) and 378 ($M+Na^+$, 61); **HRMS** (+ESI)

Found M+Na^+, 378.0941; $C_{19}H_{17}NO_6Na$ requires $M+Na^+$ 378.0954; **HPLC** t_R 10.5 (85 %).

Carbonate (181)

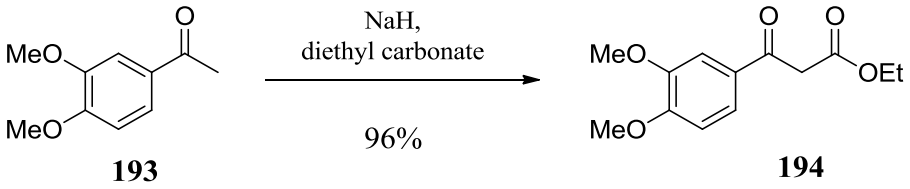
Decomposes in air at r.t. to **179**

R_f [PE-EtOAc 50:50] 0.26; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 7.50-7.47 (4H, m, Ph), 7.43 (1H, d, *J* 8.0 Hz, C(3)H), 7.38-7.30 (9H, m, Ph), 6.70 (1H, s, C(5)H), 6.24 (1H, d, *J* 8.0 Hz, C(4)H), 5.42 (2H, s, CH_2Ph), 5.35 (2H, s, CH_2Ph), 3.91 (3H, s, OCH_3) and 3.82 (3H, s, OCH_3); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 158.1− (C1=O), 157.8− (C6 or C7), 152.8− (NCO_2Bn or OCO_2Bn), 152.5− (NCO_2Bn or OCO_2Bn), 145.0− (C8), 141.6− (C6 or C7), 135.0− (Ph), 134.5 (Ph), 128.5+ (Ph), 128.5+ (Ph), 128.4+ (Ph), 128.3+ (Ph), 128.2+ (Ph), 128.0+ (Ph), 127.2+ (C3), 113.5− (C4a or C8a), 108.5− (C4a or C8a), 106.5+ (C4), 105.3+ (C5), 70.4− (CH_2Ph), 69.8− (CH_2Ph) , 61.4+ (OCH_3) and 56.1+ (OCH_3); **MS** (+ESI) *m/z* 356 (M-BnOCO_2^-+$2H^+$, 100 %), 490 (M+H^+, 27), 512 (M+Na^+, 36); **HRMS** (+ESI) Found M+H^+, 490.1498; $C_{27}H_{24}NO_8$ requires $M+H^+$ 490.1502.

5.3. SYNTHESIS OF ABC-RING ANALOGUES

5.3.1. Synthesis of the Dimethoxy Analogue

Ethyl 3-(3',4'-dimethoxyphenyl)-3-oxopropanoate (194)



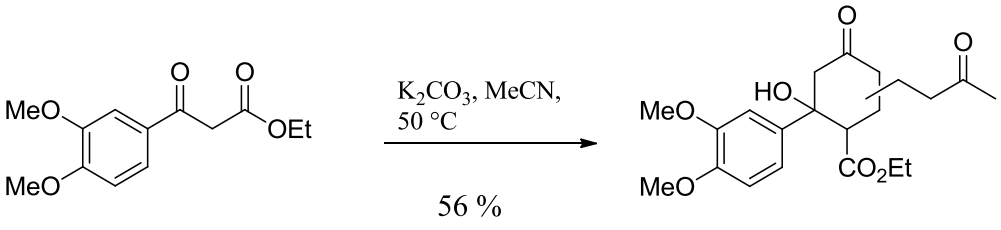
193 **194**

Following the procedure reported by Arnould *et al.*,[131] NaH (60 % dispersion in mineral oil) (3 g, 75 mmol) was added portionwise over 3 mins to a stirred solution of 3,4-dimethoxyacetophenone **193** (9 g, 50 mmol) in diethyl carbonate (100 mL) at 0 °C under N_2, then the reaction was heated at 80 °C for 1 ½ hrs. After cooling to r.t., the reaction was quenched with saturated aqueous NH_4Cl (30 mL) and H_2O (300 mL), then extracted with EtOAc (3 x 125 mL). The combined organic fractions were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo*. After column chromatography [silica, PE-EtOAc 65:35] β-ketoester **194** (12.13 g, 96 %) was isolated as a pale yellow oil.

R_f [PE-EtOAc: 30:70] 0.93; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 7.51 (1H, dd, *J* 8.0 and 2.0 Hz, C(6')H), 7.49 (1H, d, *J* 2.0 Hz, C(2')H), 6.85 (1H, d, *J* 8.0 Hz, C(5')H), 4.17 (2H, q, *J* 7.0 Hz, OCH_2CH_3), 3.91 (5H, s, OCH_3 and $C(2)H_2$), 3.89 (3H, s, OCH_3) and 1.22 (3H, t, *J* 7.0 Hz, OCH_2CH_3); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 190.9− (C3=O), 167.6− (CO_2Et), 153.7− (C3'-O or C4'-O), 149.0− (C3'-O or C4'-O), 129.2− (C1'), 123.4+ (C(Ar)-H), 110.2+ (C(Ar)-H), 110.0+ (C(Ar)-H), 61.3− (OCH_2CH_3), 56.0+ (OCH_3), 55.9+ (OCH_3), 45.6− (C2) and 14.0+ (OCH_2CH_3).

Spectroscopic data is consistent with that reported by Jung *et al.*[248]

Ethyl 2-(3,4-dimethoxyphenyl)-2-hydroxy-4-oxo-1-(3-oxobutyl)cyclohexanecarboxylate or ethyl 2-(3,4-Dimethoxyphenyl)-2-hydroxy-4-oxo-3-(3-oxobutyl)cyclohexanecarboxylate or ethyl 2-(3,4-Dimethoxyphenyl)-2-hydroxy-4-oxo-5-(3-oxobutyl)cyclohexanecarboxylate (204)

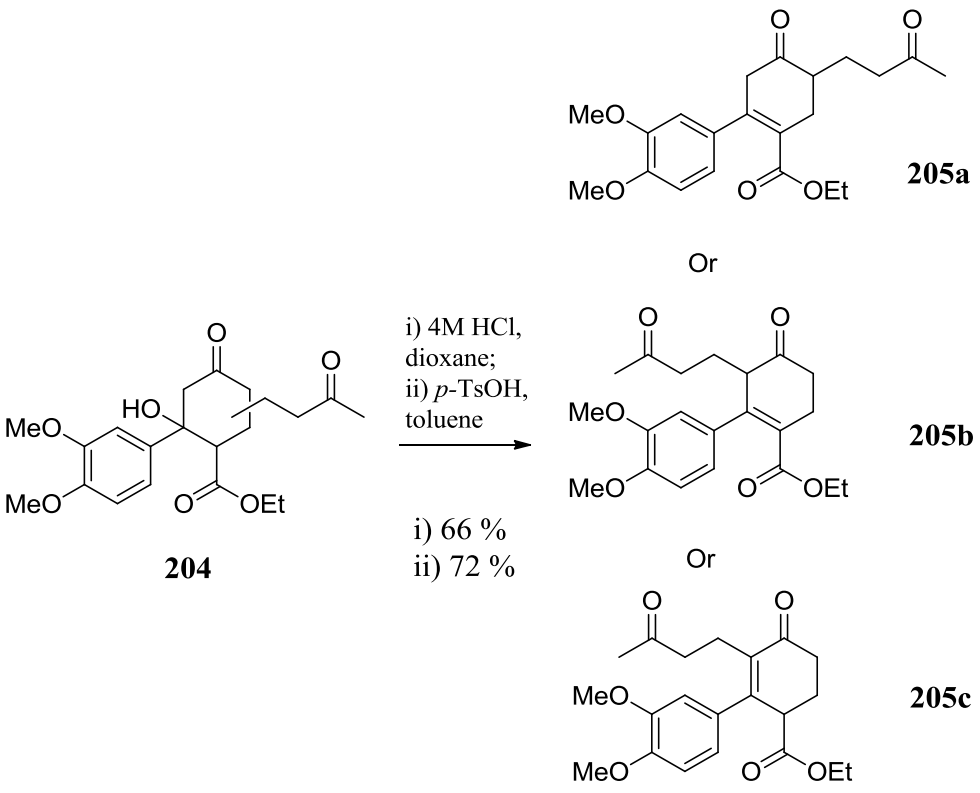


194 **204**

K_2CO_3 (345 mg, 2.5 mmol) was added to a vigorously stirred solution of β-ketoester **194** (252 mg, 1 mmol) in anhydrous MeCN (5 mL) at r.t. under N_2. After 5 mins, MVK (202 μL, 2.5 mmol) was added and the reaction stirred for 24 hrs at 50 °C. The reaction was quenched with saturated aqueous NH_4Cl (15 mL) then extracted with EtOAc (3 x 15 mL). The combined organic fractions were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo*. After column chromatography [silica, PE-EtOAc gradient from 80:20 to 40:60] the product **204** (221 mg, 56 %) was isolated as a yellow oil.

R_f [PE-EtOAc 50:50] 0.49; **IR** ν_{max}(thin film) 3506 (OH), 2968 (CH), 2841 (CH), 1731 (C=O), 1672 (C=O), 1595 (C=C), 1515 (C=C), 1463, 1416, 1264 (C-O), 1228 (C-O), 1148, 1023 and 764; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 7.57-7.44 (2H, m, Ar C-H), 6.82 (1H, d, *J* 8.0 Hz, Ar C-H), 4.18-4.08 (2H, m, O*CH*$_2$CH$_3$), 3.92 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.01 (1H, dd *J* 13.0 and 3.5 Hz), 2.60 (1H, td, *J* 14.0 and 4.0 Hz) 2.45 (1H, *J* 13.0 and 3.0 Hz) 2.32-2.16 (5H, m), 2.03 (2H, t, *J* 6.5 Hz), 1.58 (1H, dt, *J* 14.0 and 3.5 Hz) 1.24 (1H, t, *J* 7 Hz) and 1.20-1.10 (5H, m); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 215.4− (ketone C=O), 196.1− (ketone C=O), 173.3− CO_2Et), 153.1−, 149.0−, 127.8−, 123.0+, 111.2+, 109.9+, 68.8−, 61.8−, 56.6−, 56.0+, 55.9+, 52.6+, 34.7−, 31.3+, 30.9−, 28.7+, 27.2− and 13.9+; **MS** (+ESI) *m/z* 375 (M-H_2O+H^+, 100 %); **HRMS** (+ESI) Found M-H_2O+H^+, 375.1801; $C_{21}H_{26}O_6$ requires *M-H_2O+H^+* 375.1802.

Ethyl 3',4'-dimethoxy-5-oxo-4-(3-oxobutyl)-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carboxylate, or ethyl 3',4'-dimethoxy-5-oxo-6-(3-oxobutyl)-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carboxylate, or ethyl 3',4'-dimethoxy-5-oxo-6-(3-oxobutyl)-2,3,4,5-tetrahydro-[1,1'-biphenyl]-2-carboxylate (205)



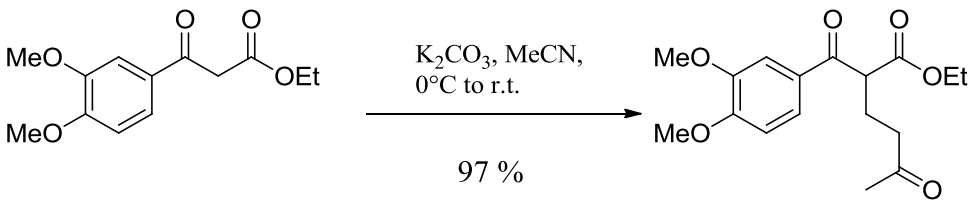
Method A: 4M HCl in dioxane (0.25 mL) was added dropwise to a stirred solution of alcohol **204** (119 mg, 0.30 mmol) in THF at r.t. and stirred for 3 ½ hrs, then the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic fractions were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo*. After column chromatography [silica, PE-EtOAc gradient from 90:10 to 70:30] the product **205** (74 mg, 66 %) was isolated as a yellow oil.

Method B: p-TsOH (18 mg, 0.06 mmol) was added to a stirred solution of **204** (130 mg, 0.34 mmol) in anhydrous toluene (3.5 mL) at r.t. under N_2 and the reaction was heated at reflux for 1 hr. The reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL) then extracted with EtOAc (3 x 10 mL). The combined organic fractions were washed with brine (15 mL), dried over anhydrous Na_2SO_4,

filtered and the solvent removed *in vacuo*. After column chromatography [silica, PE-EtOAc gradient from 100:0 to 75:25] the product **205** (89 mg, 72 %) was isolated as a yellow oil.

R_f [PE-EtOAc 50:50] 0.58; **IR** ν_{max}(KBr disc) 2951, 2856 (CH), 1730 (C=O), 1675 (C=O), 1589, 1515, 1416, 1348, 1266 (C-O), 1221, 1151, 1022 and 765; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 7.49 (1H, d, *J* 8.0 Hz, C(Ar)H), 7.48 (1H, s, C(Ar)H), 6.82 (1H, d, *J* 8.0 Hz, C(Ar)H), 4.12 (2H, q, *J* 7.0 Hz, O*CH*$_2$CH$_3$), 3.91 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 2.89 (1H, d, *J* 17.0 Hz), 2.72 (1H, d, *J* 17.0 Hz), 2.28 – 2.00 (7H, m), 1.84 (3H, s, CH_3C=O) and 1.09 (3H, t, *J* 7.0 Hz, OCH_2*CH*$_3$); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 202.8− (ketone C=O), 194.2− (ketone C=O), 173.3− (CO_2Et), 153.1−, 149.0−, 139.6−, 130.6−, 127.8−, 122.7+, 111.3+, 109.9+, 61.6−, 56.1−, 56.0+, 55.9+, 32.9−, 30.1−, 29.9+, 28.4−, 21.2+ and 13.9+; **MS** (+ESI) *m/z* 375 ($M+H^+$, 100 %); **HRMS** (+ESI) Found $M+H^+$, 375.1795; $C_{21}H_{26}O_6$ requires $M+H^+$ 375.1802.

Ethyl 2-(3',4'-dimethoxybenzoyl)-5-oxohexanoate (202)

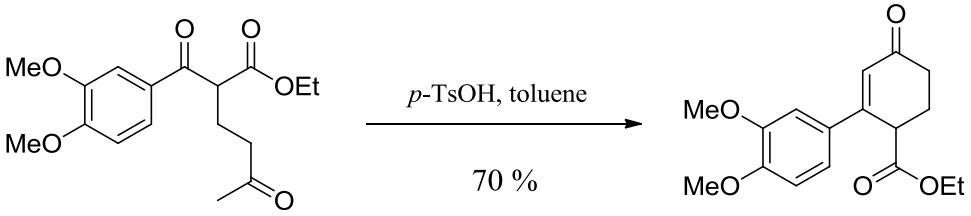


194 **202**

K_2CO_3 (834 mg, 5.5 mmol) was added to a vigorously stirred solution of β-ketoester **194** (1.26 g, 5 mmol) in anhydrous MeCN (20 mL) at 0 °C under N_2. After 10 mins, MVK (446 μL, 5.5 mmol) was added and the reaction allowed to warm to r.t. and stirred for a further 2 ½ hrs. The reaction was quenched with saturated aqueous NH_4Cl (20 mL) then extracted with EtOAc (3 x 20 mL). The combined organic fractions were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo*. After column chromatography [silica, PE-EtOAc gradient from 90:10 to 60:40] the Michael addition product **202** (1.566 g, 97 %) was isolated as a pale yellow oil.

R_f [PE-EtOAc 50:50] 0.53; **IR** ν_{max}(Thin film) 2976, 2938, 2841, 1731 (C=O), 1721 (C=O), 1673 (C=O), 1594, 1514, 1463, 1418, 1368, 1345, 1266, 1155 and 1021; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 7.69 (1H, dd, *J* 8.5 and 1.5 Hz, C(6')H), 7.59 (1H, d, *J* 1.5 Hz, C(2')H), 6.90 (1H, d, *J* 8.5 Hz, C(5')H), 4.41 (1H, dd, *J* 8.0 and 6.5 Hz, C(2)H), 4.14 (2H, q, *J* 7.0 Hz, OC*H*$_2$CH$_3$), 3.94 (6H, s, OCH_3), 2.62-2.54 (2H, m, C(4)H_2), 2.25-2.17 (2H, m, C(3)H_2), 2.12 (3H, s, C(6)H_3) and 1.18 (3H, t, *J* 7.0Hz, OCH_2CH_3); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 208.0− (CH_3*C*5=O), 193.8− (Ar*C*=O), 170.0− (CO_2Et), 153.8− (*C*(Ar)-O), 149.1− (*C*(Ar)-O), 129.0− (*C*1'-C), 123.6+ (*C*(Ar)-H), 110.7+ (*C*(Ar)-H), 110.1+ (*C*(Ar)-H), 61.3− (OCH_2CH_3), 56.1+ (OCH_3), 56.0+ (OCH_3), 52.3+ (C2), 40.5− (C4), 30.0+ (C6), 23.0− (C3) and 14.6+ (OCH_2CH_3); **MS** (+ESI) *m/z* 323 ($M+H^+$, 29 %) and 345 ($M+Na^+$, 100 %); **HRMS** (+ESI) Found $M+H^+$, 323.1491; $C_{17}H_{23}O_6$ requires $M+H^+$ 323.1495.

Ethyl 2-(3,4-dimethoxyphenyl)-4-oxocyclohex-2-enecarboxylate (206)



202 **206**

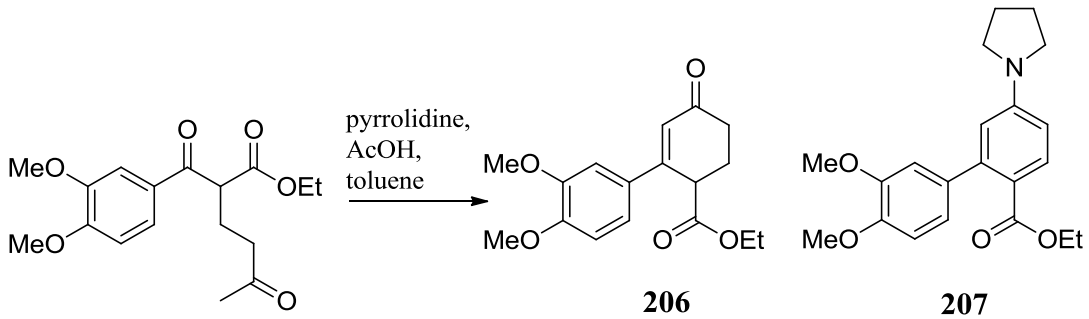
Method A: Following the procedure reported by Nour *et al.*,[87] pyrrolidine (33 μL, 0.4 mmol) and AcOH (27 μL, 0.475 mmol) were added to a stirred solution of Michael adduct **202** (160 mg, 0.5 mmol) in refluxing toluene (1 mL) under N_2. After 2 ½ hrs, the reaction was cooled to r.t. and H_2O (20 mL) was added, then extracted with EtOAc (3 x 15 mL). The combined organic fractions were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo*. After column chromatography [silica, PE-EtOAc gradient from 85:15 to 75:25] cyclohexenone **206** (79 mg, 52 %) was isolated as an oil.

Method B: *p*-TsOH (288 mg, 1.2 mmol) was added to a stirred mixture of Michael adduct **202** (975 g, 3.0 mmol) and activated 3Å molecular sieves in anhydrous toluene (30 mL) at r.t. under N_2 and the reaction was heated at reflux for

38 hrs. After column chromatography [silica, PE-EtOAc gradient from 80:20 to 70:30] the cyclised enone product **206** (644 mg, 70 %) was isolated as a yellow oil.

R_f [PE-EtOAc 50:50] 0.30; **IR** ν_{max}(thin film) 2938, 2839 (C-H), 1728 (C=O), 1661 (C=O), 1597, 1576, 1518 (C=C), 1463, 1419, 1328, 1252 (C-O), 1151 and 1022; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 7.10 (1H, dd, *J* 8.0 and 2.0 Hz, C(6')H), 7.05 (1H, d, *J* 2.0 Hz, C(2')H), 6.87 (1H, d, *J* 8.0 Hz, C(5')H), 6.46 (1H, s, C(3)H), 4.11 (2H, q, *J* 7.0 Hz, OCH_2CH_3), 3.97-9.93 (1H, m, C(1)HCO_2Et), 3.90 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 2.66-2.59 (1H, m, C(5)H_AH_B), 2.50-2.44 (2H, m, C(5)H_AH_B and C(6)H_AH_B), 2.43-2.35 (1H, m, C(6)H_AH_B), 1.15 (3H, t, *J* 7.0 Hz, OCH_2CH_3); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 198.6− (C(4)=O), 171.7− (CO_2Et), 154.9− (C1'), 151.0− (C3'-O or C4'-O), 149.1− (C3'-O or C4'-O), 130.1− (C2), 125.5+ (C3), 119.6+ (C6'), 110.9+ (C2'), 109.1+ (C5'), 61.4− (OCH_2CH_3), 55.9+ (OCH_3), 55.9+ (OCH_3), 43.3+ (C1), 33.9− (C5), 26.5− (C6) and 14.0+ (OCH_2CH_3); **MS** (+ESI) *m/z* 305 ($M+H^+$, 100 %) and 327 ($M+Na^+$, 9); **HRMS** (+ESI) Found $M+Na^+$, 327.1197; $C_{17}H_{20}O_5Na$ requires $M+Na^+$ 327.1208.

Ethyl 3',4'-dimethoxy-5-(pyrrolidin-1-yl)biphenyl-2-carboxylate (207)



206 16 %

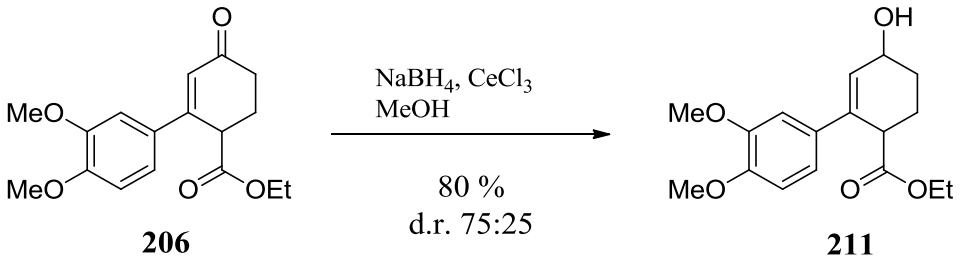
207 25 %

Following the procedure reported by Boeckman,[80] pyrrolidine (125 µL, 1.5 mmol) and AcOH (112 µL, 2 mmol) were added to a stirred solution of **202** (160 mg, 0.5 mmol) in refluxing toluene (6 mL) under N_2. After 24 hrs, the reaction was cooled to r.t. and saturated aqueous Na_2CO_3 (15 mL) was added, then extracted with EtOAc (3 x 15 mL). The combined organic fractions were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo*. After

column chromatography [silica, PE-EtOAc gradient from 100:0 to 60:40] aniline **207** (43 mg, 25 %) was isolated as an oil and cyclohexenone **206** (25 mg, 16 %) as an oil.

R_f [PE-EtOAc 50:50] 0.5; **IR** ν_{max}(thin film) 2972, 2836 (C-H), 1694 (C=O), 1600, 1505, 1463, 1383, 1281, 1244 (C-O), 1140, 1095 and 1028; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 7.87 (1H, d, *J* 9.0 Hz, C(3)H), 6.88-6.84 (3H, m, C(2')H, C(5')H and C(6')H), 6.50 (1H, dd, *J* 9.0 and 2.5 Hz, C(4)H), 6.39 (1H, d, *J* 2.5 Hz, C(6)H), 4.06 (2H, q, *J* 7 Hz, OC*H*$_2$CH$_3$), 3.91 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.36-3.33 (4H, m, NC*H*$_2$CH$_2$), 2.03-2.01 (4H, m, NCH$_2$C*H*$_2$) and 1.04 (3H, t, *J* 7 Hz, OCH$_2$C*H*$_3$); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 168.1− (C=O), 149.6− (C2), 148.1− (C3' or C4'), 148.0− (C3' or C4'), 145.0− (C1'), 136.1− (C1), 132.6− (C3), 120.5+ (C2', C5' or C6'), 116.5− (C5), 113.7+ (C6), 112.2+ (C2', C5' or C6'), 110.5+ (C2', C5' or C6'), 109.7+ (C4), 59.9− (O*C*H$_2$CH$_3$), 55.9+ (OCH_3), 55.9+ (OCH_3), 47.5− (N*C*H$_2$CH$_3$), 25.4− (NCH$_2$*C*H$_3$) and 14.0+ (OCH$_2$*C*H$_3$); **MS** (+ESI) *m/z* 356 ($M+H^+$, 100 %) and 378 ($M+Na^+$, 40); **HRMS** (+ESI) Found $M+H^+$, 356.1847; $C_{21}H_{26}NO_4$ requires $M+H^+$ 356.1862.

Ethyl 5-hydroxy-3',4'-dimethoxy-2,3,4,5-tetrahydro-[1,1'-biphenyl]-2-carboxylate (211)



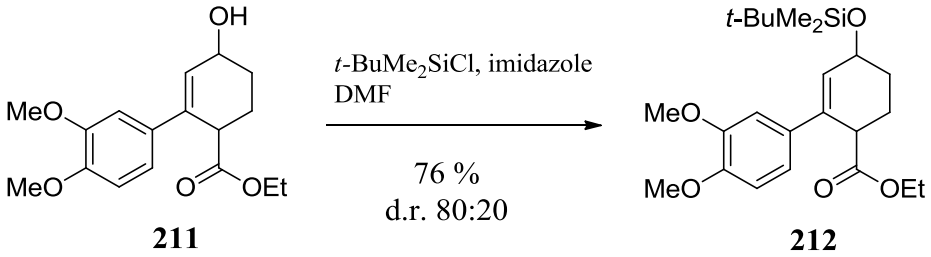
206 **211**

$CeCl_3$ (184 mg, 0.75 mmol) was added to a stirred solution of enone **206** (160 mg, 0.5 mmol) in MeOH (3 mL) at r.t. then the reaction was cooled in an ice bath and $NaBH_4$ (21 mg, 0.55 mmol) added. After 45 mins, the reaction was quenched with saturated aqueous NH_4Cl (10 mL) then extracted with EtOAc (3 x 10 mL). The combined organic fractions were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo*. After column chromatography [silica, PE-EtOAc gradient from 100:0 to 50:50] the alcohol product

211 (122 mg, 80 %) was isolated as an oil and a 75:25 mixture of diastereoisomers by ^{1}H NMR.

R_f [PE-EtOAc 50:50] 0.25; **IR** ν_{max}(thin film) 3493 (OH), 2967, 2850 (CH), 1729 (C=O), 1602, 1583, 1517 (C=C), 1463, 1250 (C-O), 1168 and 1026; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 6.95-6.93 (2H, m, C(2')H and C(6')H), 6.79 (1H, d, *J* 8.0 Hz, C(5')H), 6.17-6.15 (1H, m, C(6)H), 4.44 (0.25H, broad s, C(5)HOH), 4.36 (0.75H, broad s, C(5)HOH), 4.05-3.98 (2H, m, OCH_2CH_3), 3.88 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.69 (0.25H, t, 5.5 Hz C(2)HCO_2Et), 3.61 (0.75H, t, 5.5 Hz C(2)HCO_2Et), 2.16-1.68 (5H, m, C(3)H_2, C(4)H_2 and OH) and 1.10-1.05 (3H, m, OCH_2CH_3); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 174.0− (isomer A C=O), 173.7− (Isomer B C=O), 148.7− (Isomer A), 148.7− (Isomer B), 137.6− (Isomer B), 137.2− (Isomer A), 133.2− (Isomer B), 133.0− (Isomer A), 128.9+ (Isomer A C6, C2', C5' or C6'), 128.5+ (Isomer B C6, C2', C5' or C6'), 118.2+ (Isomer B C6, C2', C5' or C6'), 118.1+ (Isomer A C6, C2', C5' or C6'), 110.8+ (Isomer B C6, C2', C5' or C6'), 110.8+ (Isomer A C6, C2', C5' or C6'), 109.2+ (C6, C2', C5' or C6'), 109.2+ (C6, C2', C5' or C6'), 66.1+ (Isomer A C5HOH), 65.6+ (Isomer B C5HOH), 60.7− (OCH_2CH_3), 60.6− (OCH_2CH_3), 55.8+ (OCH_3), 55.8+ (OCH_3), 43.8+ (Isomer B $C2HCO_2Et$), 43.5+ (Isomer A $C2HCO_2Et$), 29.2− (Isomer B C3 or C4), 28.9− (Isomer A C3 or C4), 24.2− (Isomer A C3 or C4), 23.4− (Isomer B C3 or C4) and 14.0+ (OCH_2CH_3); **MS** (+ESI) *m/z* 329 ($M+Na^+$, 100 %); **HRMS** (+ESI) Found $M+Na^+$, 329.1352; $C_{17}H_{22}O_5Na$ requires $M+Na^+$ 329.1365.

Ethyl 5-((tert-butyldimethylsilyl)oxy)-3',4'-dimethoxy-2,3,4,5-tetrahydro-[1,1'-biphenyl]-2-carboxylate 212



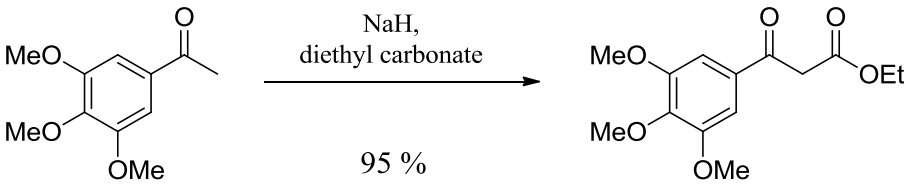
211 **212**

t-Butyldimethylsilyl chloride (497 mg, 3.3 mmol) was added to a stirred solution of cyclohexenol **211** (900 mg, 3 mmol) and imidazole (225 mg, 3.3 mmol) in anhydrous DMF (6 mL) at 0 °C under N_2 and the reaction stirred for 5 mins then was allowed to warm to r.t.. After 4 hrs, the reaction was quenched with saturated aqueous NH_4Cl (25 mL) then extracted with EtOAc (3 x 20 mL). The combined organic fractions were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo*. After column chromatography [silica, PE-EtOAc gradient from 80:20 to 20:80] the silyl ether **212** (960 mg, 76 %) was isolated as an oil and a 4:1 mixture of diastereoisomers by ^{1}H NMR.

R_f [PE-EtOAc 30:70] 0.77; **IR** ν_{max}(thin film) 2932, 2856 (CH), 1732 (C=O), 1603, 1583, 1517 (C=C), 1463, 1365, 1250 (C-O), 1168, 1084 (Si-C), 1028, 836, 774; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 6.90 (1H, broad s, C(2')H), 6.87 (1H, d, *J* 7.0 Hz, C(5')H), 6.79 (1H, dd, *J* 7.0 and 2.5 Hz, C(6')H), 6.00 (0.8H, broad s, C(6)H), 5.98 (0.2H, broad s, C(6)H), 4.46-4.42 (0.2H, m, C(5)HOSi), 4.39-4.34 (0.8H, m, C(5)HOSi), 4.02-3.70 (2H, m, O*C*$H_2$$CH_3$), 3.88 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.68 (0.2H, t, *J* 5.0 Hz, C(2)HCO_2Et), 3.56 (0.2H, t, *J* 5.0 Hz, C(2)HCO_2Et), 2.21-2.12 (1H, m, C(3)H_AH_B or C(4)H_AH_B), 2.04-1.89 (1H, m, C(3)H_AH_B or C(4)H_AH_B), 1.83-1.78 (2H, m, C(3)H_2 or C(4)H_2), 1.07-1.03 (3H, m, OCH_2CH_3), 0.93 (7.2H, s, $C(CH_3)_3$), 0.93 (1.8H, s, $C(CH_3)_3$), 0.13 (2.4H, s, $SiCH_3$), 0.11 (2.4H, s, $SiCH_3$), 0.10 (0.6H, s, $SiCH_3$) and 0.09 (0.6H, s, $SiCH_3$); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 174.2− (Isomer B C=O), 173.9− (Isomer A C=O), 148.6− (Isomer A), 148.6− (Isomer B), 136.3− (Isomer B), 135.6− (Isomer A), 133.8− (Isomer B), 133.6− (Isomer A), 130.8+ (Isomer A), 130.3+ (Isomer B), 118.3+ (Isomer B), 118.2+ (Isomer A), 110.8+, 109.4+ (Isomer A), 109.4+ (Isomer B), 67.2+ (Isomer A CHOH), 66.6+ (Isomer B CHOH), 60.5− (OCH_2CH_3), 55.8+ (OCH_3), 55.8+ (OCH_3), 44.3+ (Isomer B C2), 43.2+ (Isomer A C2), 30.2− (Isomer B), 29.1− (Isomer A), 25.9+ (Isomer A CCH_3), 25.9+ (Isomer B CCH_3), 24.4− (Isomer A), 24.1− (Isomer B), 18.3− (Isomer A CCH_3), 18.2− (Isomer B CCH_3), 14.0+ (OCH_2CH_3), -4.32+ (Isomer A $SiCH_3$),), -4.36+ (Isomer B $SiCH_3$) and -4.57+ ($SiCH_3$); **MS** (+ESI) *m/z* 289 (M-^{t}BuMe$_2$SiOH+H$^+$, 100 %) and 443 (M+Na$^+$, 46); **HRMS** (+ESI) Found M+Na$^+$, 443.2205; $C_{23}H_{36}O_5NaSi$ requires $M+Na^+$ 443.2230.

5.3.2. Synthesis of the Trimethoxy-Analogue

Ethyl 3-(3',4',5'-trimethoxyphenyl)-3-oxopropanoate (216)



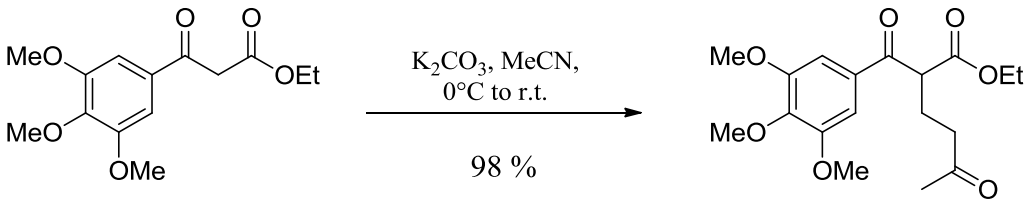
215 **216**

NaH (60 % dispersion in mineral oil) (3.0 g, 75 mmol) was added portionwise over 3 mins to a stirred solution of 3,4,5-trimethoxyacetophenone **215** (10.5 g, 50 mmol) in diethyl carbonate (100 mL) at 0 °C under N_2, then the reaction was heated at 80 °C for 1 ½ hrs. On cooling, the reaction was quenched with saturated aqueous NH_4Cl (30 mL) and water (200 mL), then extracted with EtOAc (3 x 120 mL). The combined organic fractions were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo*. After column chromatography [silica, PE-EtOAc gradient from 100:0 to 40:60] β-ketoester **216** (13.8 g, 95 %) was isolated as a pale yellow solid.

R_f [PE-EtOAc 50:50] 0.43; **Mp** 84-88 °C (from EtOAc); lit.,[249] 87-88 °C (from EtOH); **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 7.20 (2H, s, C(2')H and C(6')H), 4.20 (2H, q, *J* 7.0 Hz, OCH_2CH_3), 3.95 (2H, s, $C(2)H_2$), 3.91 (3H, s, OCH_3), 3.90 (6H, s, OCH) and 1.25 (3H, t, *J* 7.0 Hz, OCH_2CH_3); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 191.2− (C3=O), 167.5− (CO_2Et), 153.1− (C(Ar)-O), 143.1− (C(Ar)-O), 131.1− (C1'-C), 106.1+ (C2'-H), 61.5− (OCH_2CH_3), 61.0+ (OCH_3), 56.3+ (OCH_3), 46.1− (C2) and 14.1+ (OCH_2CH_3);

Spectroscopic data is consistent with that reported by Lawrence *et al.*[250]

Ethyl 2-(3',4',5'-trimethoxybenzoyl)-5-oxohexanoate (217)

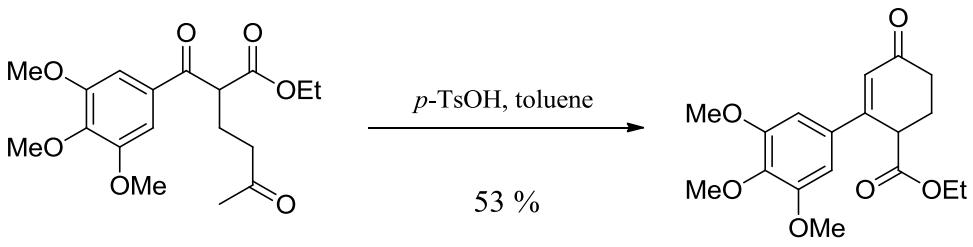


216 **217**

K_2CO_3 (4.1 g, 29.7 mmol) was added to a vigorously stirred solution of β-ketoester **216** (7.60 g, 27 mmol) in anhydrous MeCN (120 mL) at 0 °C under N_2. After 10 mins, MVK (2.41 mL, 29.7 mmol) was added and the reaction allowed to warm to r.t.. After 1 ½ hrs, the reaction was quenched with saturated aqueous NH_4Cl (20 mL), then extracted with EtOAc (3 x 100 mL). The combined organic fractions were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo*. After column chromatography [silica, PE-EtOAc gradient from 90:10 to 50:50] the product **217** (9.30 g, 98 %) was isolated as a pale yellow oil.

R_f [PE-EtOAc 50:50] 0.53; **IR** ν_{max}(Thin film) 2979, 2840, 1731 (C=O), 1722 (C=O), 1681 (C=O), 1584, 1505, 1455, 1416, 1337, 1234, 1126 and 1002; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 7.37 (2H, s, C(2')H and C(6')H), 4.43 (1H, dd, *J* 9.0 and 6.0 Hz, C(2)H), 4.19-4.13 (2H, m, OCH_2CH_3), 3.94 (6H, s, OCH_3), 3.92 (3H, s, OCH_3), 2.64-2.55 (2H, m, $C(4)H_2$), 2.28-2.15 (2H, m, $C(3)H_2$), 2.13 (3H, s, $C(6)H_3$) and 1.20 (3H, t, *J* 7.5 Hz, OCH_2CH_3); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 208.0− (C5=O), 194.2− (Ar*C*=O), 170.0− (CO_2Et), 153.1− (C(Ar)-O), 143.0− (C(Ar)-O), 130.8− (C1'), 106.2+ (C2' and C6'), 61.4− (OCH_2CH_3), 60.9+ (OCH_3), 56.3+ (OCH_3), 52.6+ (C2), 40.5− (C4), 30.0+ (C6), 23.0− (C3) and 14.0+ (OCH_2CH_3); **MS** (+ESI) *m/z* 353 ($M+H^+$ 100 %) and 375 ($M+Na^+$, 69); **HRMS** (+ESI) Found $M+H^+$, 353.1601; $C_{18}H_{25}O_7$ requires $M+H^+$ 353.1600.

Ethyl 2-(3',4',5'trimethoxyphenyl)-4-oxocyclohex-2-enecarboxylate (218)

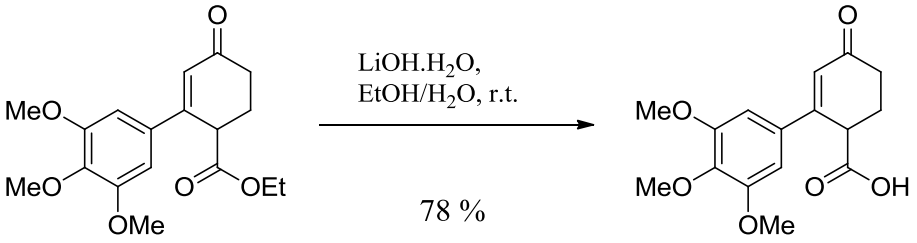


217 **218**

p-TsOH (2.85 g, 15.2 mmol) in toluene (225 mL) was heated at reflux with azeotropic removal of water using Dean-Stark trap under Ar for 1 hr, then β-ketoester **217** (12.31 g, 34.9 mmol) was added and heated continued for a further 24 hrs. After cooling to r.t., the solvent was removed *in vacuo* and column chromatography [silica, PE-EtOAc gradient from 100:0 to 70:30] afforded the enone product **218** (6.18 g, 53 %) as a pale yellow solid.

R_f [PE-EtOAc 50:50] 0.52; **Mp** 107-110 °C (from Et_2O); **IR** ν_{max}(thin film) 2938, 2839 (C-H), 1728 (C=O), 1661 (C=O), 1597, 1576, 1518 (C=C), 1463, 1419, 1328, 1252 (C-O), 1151, 1022; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 6.72 (2H, s, C(2')H), 6.45 (1H, s, C(3)H), 4.13 (2H, q, *J* 7.0 Hz, OCH_2CH$_3$), 3.93 (1H, t, *J* 4.5 Hz, C(1)H), 3.87 (9H, s, OCH_3), 2.69-2.61 (1H, m, C(5)H_AH$_B$), 2.51-2.36 (3H, m, C(5)H$_A$$H_B$ and C(6)H_2) and 1.14 (3H, t, *J* 7.0 Hz, OCH_2CH_3); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 198.5− (C4=O), 171.7− (*C*O_2Et), 155.3− (C1'), 153.3− (C3'), 139.9− (C4'), 133.2− (C1), 126.7+ (C6), 103.8+ (C2'), 61.5− (O*C*H_2CH$_3$), 60.9+ (C(4')O*C*H$_3$), 56.2+ (C(3')O*C*H$_3$), 43.7+ (C1), 34.0− (C5), 26.6− (C6) and 14.1+ (OCH$_2$*C*H$_3$); **MS** (+ESI) *m/z* 335 (M+H$^+$, 100 %); **HRMS** (+ESI) Found M+H$^+$, 335.1495; $C_{18}H_{22}O_6$ requires $M+H^+$ 335.1495; **HPLC** t_R 14.7 (98 %).

2-(3,4',5'-Trimethoxyphenyl)-4-oxocyclohex-2-enecarboxylic acid (219)

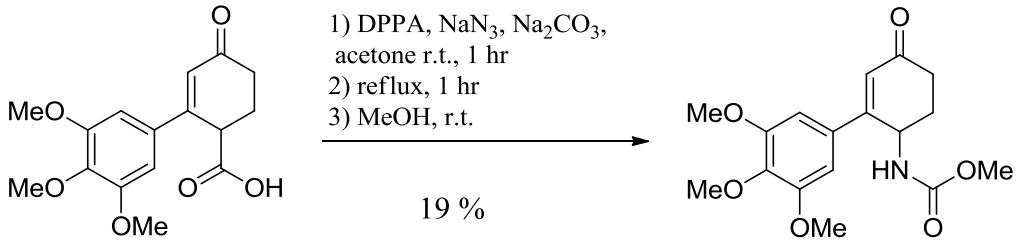


218 **219**

LiOH.H_2O (1.05 g, 25 mmol) was added to a stirred suspension of ester **218** (1.67 g, 5 mmol) in 1:1 EtOH/H_2O (25 mL) at 0 °C then the reaction was allowed to warm to r.t. After 45 mins, the reaction was diluted with H_2O (20 mL) and washed with Et_2O (3 x 20 mL). The aqueous fraction was cooled to 0 °C and acidified to pH 2 with 6M HCl, then extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo* to afford the acid **219** (1.19 g, 78 %) as a brown oil without further purification.

R_f [CH_2Cl_2-MeOH 90:10] 0.41; **IR** ν_{max}(thin film) 2938, 2839 (C-H), 1728 (C=O), 1661 (C=O), 1597, 1576, 1518 (C=C), 1463, 1419, 1328, 1252 (C-O), 1151, 1022; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 6.75 (2H, s, C(2')H), 6.50 (1H, s, C(3)H), 3.99 (1H, dd, *J* 4.5, 4.0 Hz, C(1)H), 3.87 (3H, s, C(4')OCH_3), 3.86 (6H, s, C(3')OCH_3), 2.71-2.63 (1H, m, C(5)H_AH_B) and 2.54-2.40 (3H, m, C(5)H_AH_B and C(6)H_2); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 198.8− (C4=O), 176.4− (CO_2H), 154.7− (C1'), 153.4− (C3'), 140.2− (C4'), 132.6− (C2), 126.7+ (C3), 103.9+ (C2'), 60.9+ (C(4')OCH_3), 56.2+ (C(3')OCH_3), 42.8+ (C1), 33.6− (C5) and 26.3− (C6).

Methyl (3',4',5'-trimethoxy-5-oxo-2,3,4,5-tetrahydro-[1,1'-biphenyl]-2-yl)carbamate (223)

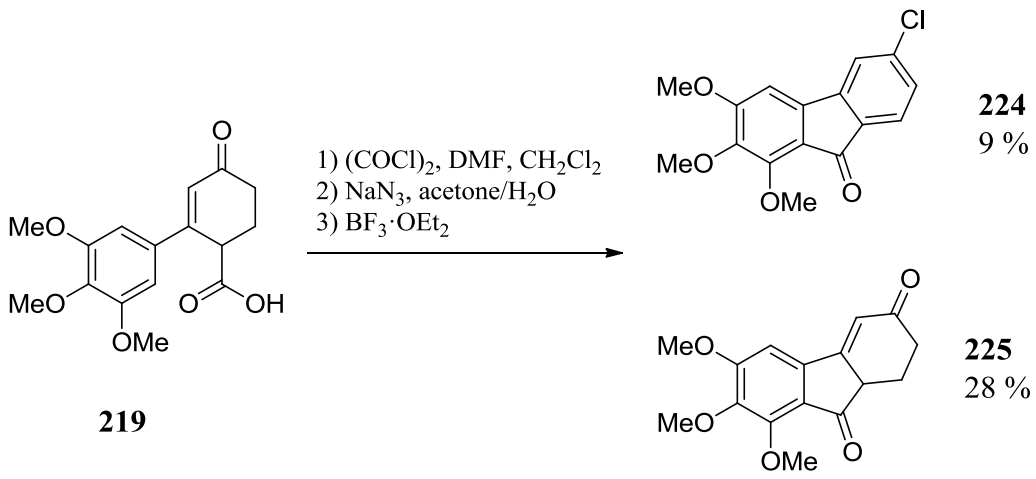


219 **223**

Diphenylphosphoryl azide (172 µL, 0.78 mmol) was added to a vigorously stirred solution of acid **219** (130 mg, 0.39 mmol), Na_2CO_3 (64 mg, 0.60 mmol) and NaN_3 (130 mg, 2 mmol) in anhydrous acetone (3 mL) at r.t. under Ar. After 1 hr, the reaction was heated at reflux for 1 hr. The solvent was removed *in vacuo*, MeOH (4 mL) added and the reaction stirred at r.t. for 16 hrs. The reaction was quenched with saturated aqueous $NaHCO_3$ (15 mL) and extracted with EtOAc (3 x 15 mL). The combined organic fractions were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo*. After column chromatography [silica, PE-EtOAc gradient from 100:0 to 0:100] the methyl carbamate **223** (25 mg, 19 %) was obtained as an amorphous solid.

R_f [PE-EtOAc 50:50] 0.15; **IR** ν_{max}(thin film) 3318 (NH), 2945, 2840, 1696 (C=O), 1664 (C=O), 1578, 1508, 1452, 1416, 1345, 1244 and 1127; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 6.79 (2H, s, C(2')H), 6.38 (1H, s, C(6)H), 5.14 (1H, broad s, C(2)H), 4.91 (1H, broad d, *J* 9.0 Hz, NH), 3.88 (3H, s, C(4')OCH_3), 3.86 (6H, s, C(3')OCH_3), 3.66 (3H, s, carbamate OCH_3), 2.60-2.48 (2H, m, C(4)H_2) and 2.36-2.19 (2H, m, C(3)H_2); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 198.4− (C5=O), 157.1− (C1), 156.4− (CO_2Me), 153.4− (C3'), 140.2− (C4'), 131.0− (C1'), 126.4+ (C6), 104.2+ (C2'), 60.9+ (C(4')OCH_3), 56.2+ (C(3')OCH_3), 52.5+ (CO_2CH_3), 46.6+ (C2), 33.3− (C4) and 29.4− (C3); **MS** (+ESI) *m/z* 336 ($M+H^+$, 100 %) and 358 ($M+Na^+$, 9); **HRMS** (+ESI) Found $M+H^+$, 336.1441; $C_{17}H_{21}NO_6$ requires $M+H^+$ 336.1447.

6-Chloro-1,2,3-trimethoxyfluoren-9-one (224) and 6,7,8-trimethoxy-1H-fluorene-3,9(2H,9aH)-dione (225)



219

Oxalyl chloride (175 µL, 2 mmol) and DMF (39 µL, 0.5 mmol) were added to the acid **219** (309 mg, 1 mmol) in CH_2Cl_2 (5 mL) under Ar at 0 °C and the reaction was allowed to warm to r.t. After 1 hr, the solvent was removed and the residue dissolved in acetone (5 mL), then the solution was added dropwise over 10 mins to a stirred solution of NaN_3 (130 mg, 2 mmol) in H_2O (5 mL) at 0 °C and the biphasic mixture stirred vigorously for a further 20 mins. The reaction was diluted with H_2O (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic fractions were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo*. The orange/brown solid was treated with $BF_3{\cdot}OEt_2$ (1 mL) under Ar and the reaction stirred at r.t. for 18 hrs. The mixture was quenched with 2M NaOH (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic fractions were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo*. After column chromatography [silica, PE-EtOAc gradient from 100:0 to 40:60] the fluoren-9-one product **224** (27 mg, 9 %) was isolated as an oil and the fluoren-3,9-dione product **225** (81 mg, 28 %) as a solid.

Fluoren-9-one (224)

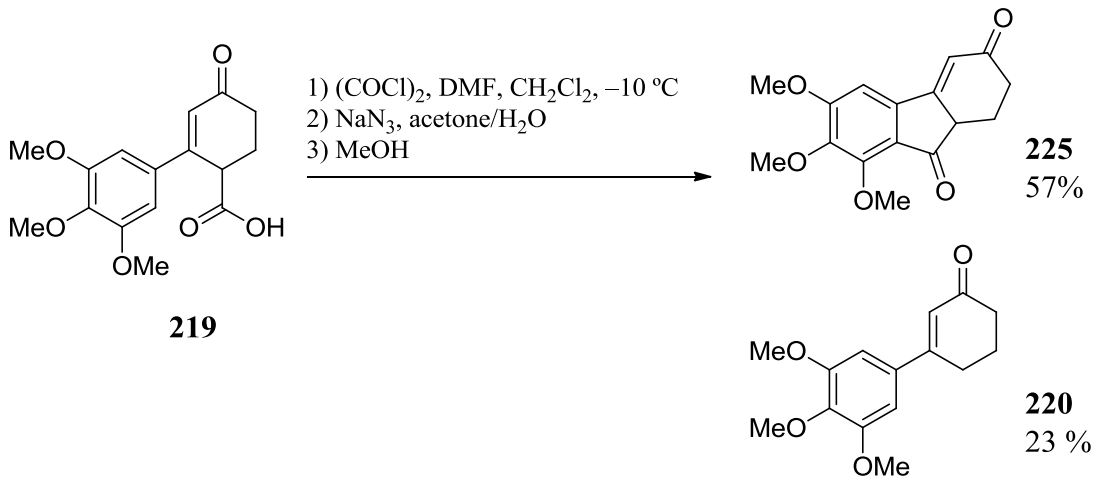
R_f [PE-EtOAc 50:50] 0.75; **IR** ν_{max}(thin film) 2940, 1704 (C=O), 1605, 1476, 1410, 1308, 1289, 1245, 1199, 1128 and 975; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 7.49

(1H, d, *J* 8.0 Hz, C(8)H), 7.38 (1H, d, *J* 1.5 Hz, C(5)H), 7.21 (1H, dd, *J* 8.0 and 1.5 Hz, C(7)H), 6.80 (1H, s, C(4)H), 4.11 (3H, s, OCH_3), 3.98 (3H, s, OCH_3) and 3.86 (3H, s, OCH_3); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 189.0− (C9=O), 159.3− (C3-O), 153.7− (C1-O), 144.6− (C4b), 142.7− (C2-O), 140.6− (C9a), 140.1− (C8a), 133.5− (C6-Cl), 128.6+ (C7), 124.7+ (C8), 120.0+ (C5), 118.4− (C4a), 62.2+ (OCH_3), 61.4+ (OCH_3) and 56.5+ (OCH_3); **MS** (+ESI) *m/z* 305 ($M+H^+$, 100 %); **HRMS** (+ESI) Found $M+H^+$, 305.0587; $C_{16}H_{14}O_4Cl$ requires $M+H^+$ 305.0575.

Fluoren-3,9-dione (225)

R_f [PE-EtOAc 50:50] 0.25; **Mp** 152-156 °C (from EtOAc); **IR** ν_{max}(thin film) 2942, 1715 (C=O), 1660 (C=O), 1586, 1480, 1335, 1255, 1137 and 1007; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 7.26 (1H, s, C(5)H), 6.32 (1H, d, *J* 2.0 Hz, C(4)H), 4.06 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.33 (1H, ddd, *J* 12.5, 5.0 and 2.0 Hz, C(9a)H), 2.66 (1H, ddd, *J* 17.5, 4.5 and 1.5 Hz, C(2)H_AH_B), 2.57 (1H, dddd, *J* 13.0, 5.0, 5.0 and 2.0 Hz, C(1)H_AH_B), 2.47 (1H, ddd, *J* 15.5, 13.0 and 4.0 Hz, C(2)H_AH_B) and 1.79 (1H, ddd, *J* 26.5, 13.5 and 4.5 Hz, C(1)H_AH_B); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 198.9− (C3=O), 196.4− (C9=O), 160.1− (C(Ar)-O), 156.9− (C8a), 151.6− (C(Ar)-O), 145.2− (C(Ar)-O), 142.0− (C4a), 123.9− (C4b), 118.1+ (C4), 100.0+ (C5), 62.2+ (OCH_3), 61.5+ (OCH_3), 56.6+ (OCH_3), 48.9+ (C9a), 37.5− (C2) and 23.2− (C1); **MS** (+ESI) *m/z* 289 ($M+H^+$, 100 %) and 311 ($M+Na^+$, 8); **HRMS** (+ESI) Found $M+H^+$, 289.1076; $C_{16}H_{17}O_5$ requires $M+H^+$ 289.1076.

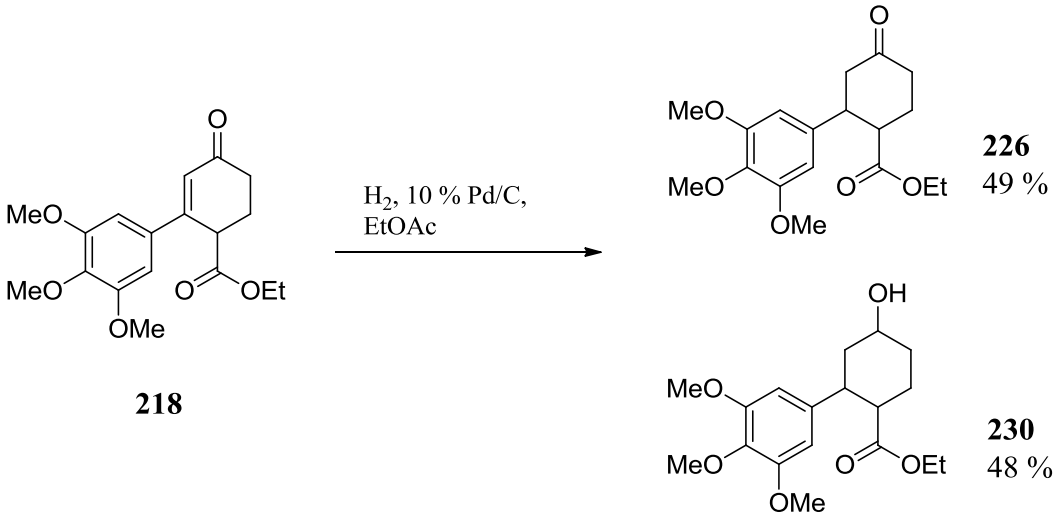
3',4',5'-Trimethoxy-5,6-dihydro-[1,1'-biphenyl]-3(4H)-one (220)



Oxalyl chloride (175 µL, 2 mmol) and DMF (39 µL, 0.5 mmol) were added to a stirred solution of acid **219** (309 mg, 1 mmol) in CH_2Cl_2 (5 mL) under Ar at −10 °C. After 1 hr, the solution was added dropwise over 10 mins to a stirred of biphasic mixture NaN_3 (130 mg, 2 mmol) in acetone/H_2O (1:1, 8 mL) at 0 °C. After 20 mins, the reaction was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (2 x 15 mL). The combined organic fractions were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo*. The orange/brown solid was treated with MeOH (5 mL) under Ar and the reaction stirred at r.t. for 24 hrs. The mixture was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic fractions were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo*. After column chromatography [silica, PE-EtOAc gradient from 100:0 to 0:100] the fluoren-3,9-dione product **225** (164 mg, 57 %) was isolated as a solid and cyclohexenone **220** (60 mg, 23 %) as an amorphous solid.

^{1}H NMR δ_H(400 MHz, $CDCl_3$) 6.75 (2H, s, C(2')H and C(6')H), 6.39 (1H, t, *J* 1.5 Hz, C(2)H), 3.88 (9H, s, OCH_3), 2.75 (2H, ddd, *J* 6.0, 6.0 and 1.5 Hz, C(4)H_2), 2.49 (2H, dd, *J* 7.0 and 6.0 Hz, C(6)H_2) and 2.19-214 (2H, m, C(5)H_2); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 199.8− (C3), 159.6− (C1), 153.3− (C3' and C5'), 140.0− (C4'), 134.4− (C1'), 125.1+ (C2), 103.8+ (C2' and C6'), 61.0+ (C(3')O*C*H_3 and C(5')O*C*H_3), 56.3+ (C(4)O*C*H_3), 37.2− (C6), 28.3− (C4) and 22.8− (C5).

Ethyl 4-oxo-2-(3',4',5'-trimethoxyphenyl)cyclohexanecarboxylate (226) and ethyl 4-hydroxy-2-(3',4',5'-trimethoxyphenyl)cyclohexanecarboxylate (230)



218

10 % Palladium on activated carbon (50 mg, 0.05 mmol) was added to a vigorously stirred solution of ester **218** (334 mg, 1 mmol) in EtOAc (5 mL). The suspension was degassed then placed under an atmosphere of H_2 at r.t. for 4 hrs. The solvent was removed *in vacuo* and after column chromatography [silica, PE-EtOAc gradient from 100:0 to 40:60] the ketone **226** (164 mg, 49 %) was isolated as an oil and the alcohol **230** (161 mg, 48 %) as a white solid.

Ketone (226)

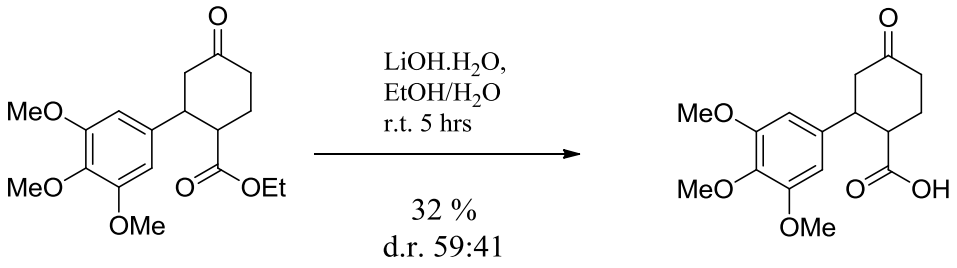
R_f [PE-EtOAc 50:50] 0.51; **IR** ν_{max}(thin film) 2939, 2839 (C-H), 1714 (ester C=O), 1590, 1510, 1462, 1423, 1331, 1251, 1176 and 1127; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 6.33 (2H, s, C(2')H), 4.00-3.95 (2H, m, OCH_2CH_3), 3.77 (9H, s, OCH_3), 3.40 (1H, dt, *J* 10.5 and 5.0, C(2)H), 3.21 (1H, ddd, *J* 14.5, 10.5 and 1.0 Hz, C(3)H_AH_B), 3.04 (1H, dt, *J* 10.0 and 5.0 Hz, C(1)H), 2.74 (1H, dddd, *J* 15.0, 10.5, 6.0 and 1.0 Hz, C(5)H_AH_B), 2.55 (1H, ddd, *J* 14.5, 5.0 and 1.0 Hz, C(3)H_AH_B), 2.34 (1H, dtd, *J* 15.0, 5.5 and 1.5 Hz, C(5)H_AH_B), 2.20 (1H, ddt, *J* 14.0, 11.5 and 6.0 Hz, C(6)H_AH_B), 2.08-2.02 (1H, m, C(6)H_AH_B) and 1.07 (3H, t, *J* 7.0 Hz, OCH_2CH_3); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 210.4− (C4=O), 173.1− (CO_2Et), 153.1− (C(Ar)-O), 137.2− (C(Ar)-O), 136.5− (C1'-C), 104.8+ (C2'-H), 60.8+ (OCH_3), 60.3− (OCH_2CH_3), 56.2+ (OCH_3), 45.2+ (C1 or C2), 44.8+ (C1 or C2), 43.7− (C3), 38.1−

(C5), 26.3− (C6) and 14.0+ (OCH_2CH_3); **MS** (+ESI) *m/z* 337 ($M+H^+$, 100 %) and 359 ($M+Na^+$, 17); **HRMS** (+ESI) Found $M+H^+$, 337.1642; $C_{18}H_{24}O_6$ requires $M+H^+$ 337.1651.

Alcohol (230)

R_f [PE-EtOAc 50:50] 0.23; **Mp** 112-115 °C (from EtOAc); **IR** ν_{max}(thin film) 3422 (OH), 2937 (C-H), 1722 (ester C=O), 1590, 1509, 1456, 1422, 1329, 1234, 1184 and 1125; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 6.43 (2H, s, C(2')H), 3.88 (2H, q, *J* 7.0 Hz, OCH_2CH_3), 3.80 (6H, s, C(3')OCH_3), 3.79 (3H, s, C(4')OCH_3), 3.74-3.69 (1H, m, C(4)HOH), 2.83-2.81 (2H, m, C(1)H and C(2)H), 2.39-2.33 (1H, m, C(3)H_AH_B), 2.08-2.02 (2H, m, C(3)H_AH_B and C(5)H_AH_B), 1.90-1.71 (4H, m, C(5)H_AH_B, C(6)H_2 and OH) and 0.99 (3H, t, *J* 7.0 Hz, OCH_2CH_3); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 173.6− (C4=O), 152.9− (C(Ar)-O), 138.6− (C1'), 136.7− (C(Ar)-O), 104.7+ (C2'), 70.8+ (C4), 60.8+ (OCH_3), 59.7− (OCH_2CH_3), 56.1+ (OCH_3), 44.8+ (C1 or C2), 43.6− (C1 or C2), 35.6− (C3), 30.7− (C6), 27.3− (C5) and 14.0+ (OCH_2CH_3); **MS** (+ESI) *m/z* 339 ($M+H^+$, 100 %) and 361 ($M+Na^+$, 18); **HRMS** (+ESI) Found $M+H^+$, 339.1808; $C_{18}H_{26}O_6$ requires $M+H^+$ 339.1808.

4-Oxo-2-(3,4,5-trimethoxyphenyl)cyclohexanecarboxylic acid (231)



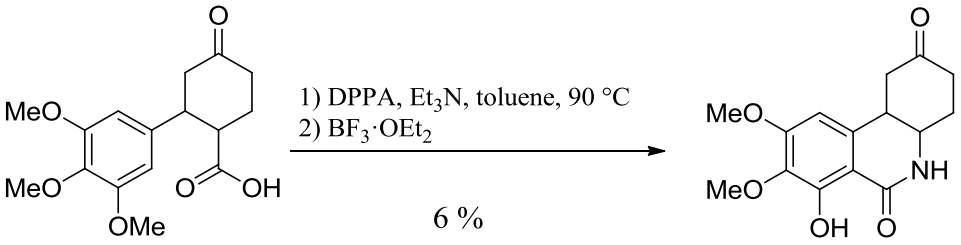
226 **231**

LiOH.H_2O (105 mg, 2.4 mmol) was added to a stirred solution of ester **226** (160 mg, 0.48 mmol) in EtOH/H_2O (1:1, 2.5 mL) and the reaction stirred for 5 hrs at r.t.. The reaction was diluted with H_2O (10 mL) and washed with Et_2O (3 x 15 mL). The aqueous fraction was acidified with 6M HCl then extracted with CH_2Cl_2 (3 x 15 mL). The combined organic fractions were dried over anhydrous Na_2SO_4, filtered

and the solvent removed *in vacuo* to afford the acid **231** (50 mg, 32 %) as white solid in a 59:41 mixture of diastereoisomers without further purification.

R_f [PE-EtOAc 50:50] 0.1; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 6.39 (1.2H, s, C(2')H), 6.36 (0.8H, s, C(2')H), 6.13 (1H, broad s, OH), 3.78 (3.6H, s, C(3')OCH_3), 3.77 (1.8H, s, C(4')OCH_3), 3.77 (1.4H, s, C(4')OCH_3), 3.73 (2.2H, s, C(3')OCH_3), 3.49 (0.4H, m, C(2)H), 3.24 (0.6H, ddd *J* 10.5, 10.5 and 5.0 Hz, C(2)H), 3.18-3.14 (0.4H, m, C(3)H_AH_B or C(5)H_AH_B), 3.11-3.08 (0.4H, m, C(1)H), 2.97 (0.6H, ddd, *J* 10.5, 10.5 and 4.0 Hz, C(1)H) and 2.70-1.93 (5H, m, C(3)H_AH_B or C(5)H_AH_B, C(3)H_2 or C(5)H_2 and C(6)H_2); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 210.8− (ketone C4=O isomer B), 208.9− (ketone C4=O isomer A), 178.2− (acid C=O isomer A), 177.7− (acid C=O isomer B), 153.3− (C3' isomer A), 153.1− (C3' isomer B), 137.4− (C1' or C4'), 137.1− (C1' or C4'), 137.1− (C1' or C4'), 136.2− (C1' or C4'), 105.0+ (C2' isomer B), 104.2+ (C2' isomer A), 60.8+ (OCH_3), 56.1+ (OCH_3 isomer A), 56.0+ (OCH_3 isomer B), 47.9+ (C1 isomer A), 47.6− (C3 or C5 isomer A), 46.1+ (C2 isomer A), 45.0+ (C1 isomer B), 44.4+ (C2 isomer B), 43.9− (C3 or C5 isomer B), 39.5− (C3 or C5 isomer A), 38.2− (C3 or C5 isomer B), 28.3− (C6 isomer A) and 25.7− (C6 isomer B);

7-Hydroxy-8,9-dimethoxy-1,3,4,4a,5,10b-hexahydrophenanthridine-2,6-dione (232)



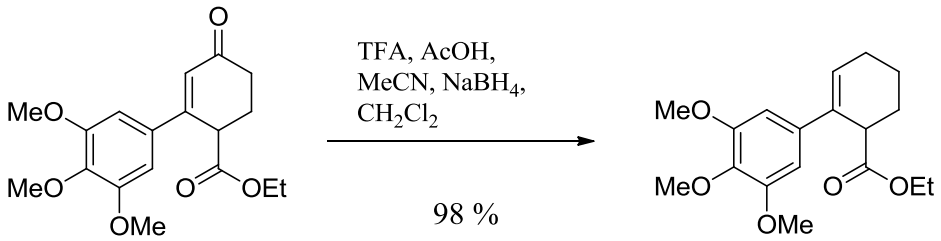
231 **232**

Diphenylphosphoryl azide (204 µL, 0.95 mmol) was added to a stirred solution of arylpropionic acid **231** (0.95 mmol) and anhydrous Et_3N (264 µL, 1.9 mmol) in anhydrous toluene (3 mL) under N_2 at r.t. then the reaction heated at 90 °C for 30 mins. After cooling to r.t., the solvent was removed *in vacuo* and the flask

cooled to 0 °C under N_2. $BF_3{\cdot}OEt_2$ (2.5 mL) was added then the reaction was allowed to warm to r.t. and stirred for 16 hrs. The reaction was quenched to pH 10 with 2M NaOH and extracted with EtOAc (2 x 20 mL). The combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo*. After column chromatography [silica, PE-EtOAc-MeOH gradient from 100:0:0 to 0:90:10] the product **232** (17 mg, 6 %) was isolated as an amorphous solid.

IR ν_{max}(thin film) 3282, 2937, 1715 (C=O), 1651, 1614, 1575, 1455, 1297, 1239 and 1129; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 12.39 (0.25H, broad s, C(7)OH), 12.24 (0.75H, broad s, C(7)OH), 6.71 (1H, broad s, N(5)H), 6.23 (0.75H, s, C(10)H), 6.18 (0.25H, s, C(10)H), 4.06-4.04 (1H, m, C(4a)H), 3.89 (3H, s, OCH_3). 3.88 (3H, s, OCH_3), 3.19-3.14 (1H, m, C(10b)H), 2.72-2.57 (2H, m, C(1)H_AH_B and C(3)H_AH_B), 2.52-2.37 (2H, m, C(1)H_AH_B and C(3)H_AH_B), 2.34-2.24 (1H, m, C(4)H_AH_B) and 2.15-2.06 (1H, m, C(4)H_AH_B); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 207.7-, 206.8-, 171.3-, 157.6-, 157.4-, 156.4-, 137.5-, 136.3, 135.8-, 129.4+, 120.2+, 103.8-, 101.3+, 98.6+, 60.7+, 56.1+, 53.8+, 49.3+, 44.2+, 41.7-, 41.6+, 40.6+, 38.6+, 35.5-, 30.1- and 28.8-; **MS** (+ESI) *m/z* 292 ($M+H^+$, 33 %) 324 ($M+Na^+$, 100); **HRMS** (+ESI) Found $M+H^+$, 292.1189; $C_{15}H_{17}NO_5$ requires $M+H^+$ 292.1179).

Ethyl 3',4',5'-trimethoxy-2,3,4,5-tetrahydro-[1,1'-biphenyl]-2-carboxylate (229)



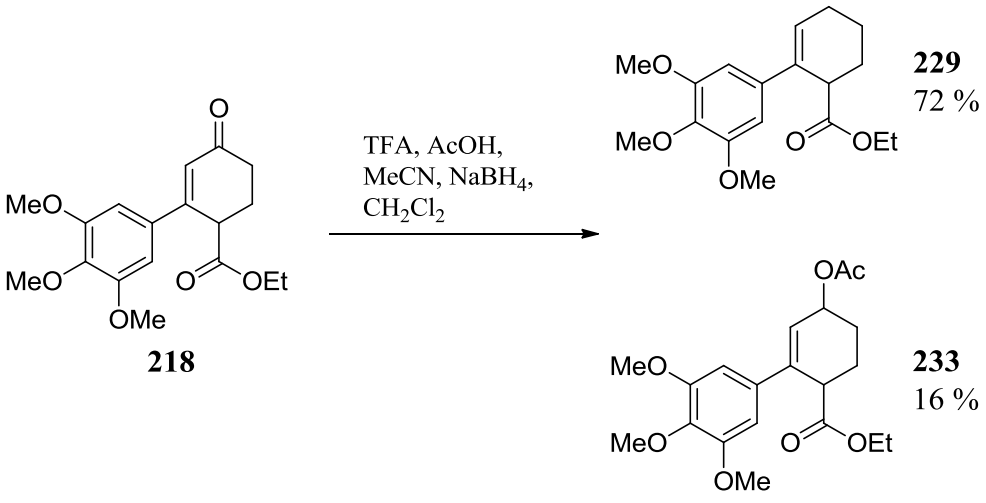
218 **229**

$NaBH_4$ (197 mg, 5.2 mmol) was added portionwise over 3 mins to a stirred solution of TFA (1.2mL), AcOH (1.2 mL) and MeCN (1.2 mL) at 0 °C under Ar. Ketone **218** (334 mg, 1 mmol) in CH_2Cl_2 (6 mL) was added and then the reaction

was allowed to warm to r.t. and stirred for 4 hrs. The reaction was neutralised with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo*. After column chromatography [silica, PE-EtOAc gradient from 100:0 to 60:40 the ester product **229** (315 mg, 98 %) was isolated as a solid.

R_f [PE-EtOAc 60:40] 0.59; **Mp** 75-80 °C (from $CHCl_3$); **IR** ν_{max}(thin film) 2937, 1731 (C=O), 1581, 1509, 1458, 1414, 1339, 1243, 1152, 1127 and 1009; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 6.53 (2H, s, C(2')H), 6.14 (1H, td, *J* 4.0 and 1.0 Hz, C(6)H), 4.06-3.97 (2H, m, OCH_2CH_3), 3.83 (6H, s, C(3')OCH_3), 3.80 (3H, s, C(4')OCH_3), 3.65-3.62 (1H, m, C(2)H), 2.88-2.20 (2H, m, C(5)H_2), 2.03-1.98 (2H, m, C(3)H_2), 1.82-1.75 (1H, m, C(4)H_AH_B), 1.69-1.60 (1H, m, C(4)H_AH_B) and 1.07 (3H, t, *J* 7.0 Hz, OCH_2CH_3); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 174.6− (C=O), 153.0− (C3'), 137.6− (C1' or C4'), 137.3− (C1' or C4'), 134.9− (C1), 128.0+ (C6), 103.1+ (C2'), 60.8+ (C(4')OCH_3), 60.4− (OCH_2CH_3), 56.1+ (C(3')OCH_3), 43.9+ (C2), 27.1− (C3), 25.5− (C5), 19.4− (C4) and 14.1+ (OCH_2CH_3); **MS** (+ESI) *m/z* 321 ($M+H^+$, 100 %); **HRMS** (+ESI) Found $M+H^+$, 321.1684; $C_{18}H_{25}O_5$ requires $M+H^+$ 321.1702.

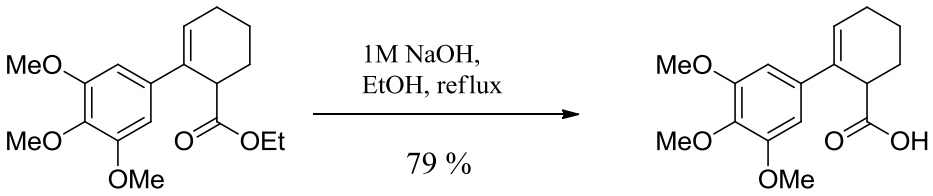
Ethyl 5-acetoxy-3',4',5'-trimethoxy-2,3,4,5-tetrahydro-[1,1'-biphenyl]-2-carboxylate (233)



$NaBH_4$ (66 mg, 1.56 mmol) was added portionwise over 3 mins to a stirred solution of TFA (0.4 mL), AcOH (0.4 mL) and MeCN (0.4 mL) at 0 °C under Ar. Ketone **218** (113 mg, 0.3 mmol) in CH_2Cl_2 (2 mL) was added and then the reaction was allowed to warm to r.t. and stirred for 90 mins. The reaction was neutralised with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo*. After column chromatography [silica, PE-EtOAc gradient from 100:0 to 60:40] the ester product **229** (69 mg, 72 %) was isolated as a white solid and acetate **233** (18 mg, 16 %) as an oil in a 0.55:0.45 mixture of diastereoisomers.

R_f [PE-EtOAc 60:40] 0.38; **IR** ν_{max}(thin film) 2940, 1731 (C=O), 1582, 1508, 1455, 1415, 1367, 1344, 1240, 1158 and 1127; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 6.56 (1.1H, s, C(2')H), 6.55 (0.9H, s, C(2')H), 6.12 (0.55H, dd, *J* 4.0 and 1.5 Hz, C(6)H), 6.09 (0.45H, dd, *J* 4.0 and 1.5 Hz, C(6)H), 5.48-5.45 (0.55H, m, C(5)H), 5.44-5.40 (0.45H, m, C(5)H), 4.06-3.99 (2H, m, OCH_2CH_3), 3.84 (6H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.73-3.69 (0.55H, m, C(2)H), 3.63-3.60 (0.45H, m, C(2)H), 2.20-1.74 (7H, m, CH_3C=O, C(3)H_2 and C(4)H_2) 1.07 (1.35H, t, *J* 7.0 Hz, OCH_2CH_3) and 1.07 (1.65H, t, *J* 7.0 Hz, OCH_2CH_3); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 173.6− (CO_2Et isomer B), 173.3− (CO_2Et isomer A), 170.9− (CH_3C=O isomer B), 170.6− (CH_3C=O isomer A), 153.1− (C3'), 139.9− (C1 isomer A), 139.7− (C1 isomer B), 138.1− (C4'), 135.9− (C1' Isomer A), 135.8− (C1' isomer B), 125.5+ (C6 isomer B), 125.3+ (C6 isomer A), 103.5+ (C2' isomer A), 103.4+ (C2' isomer B), 68.1+ (C5 isomer B), 68.0+ (C5 isomer A), 60.9+ (C(4')OCH_3), 60.8− (OCH_2CH_3), 56.2+ (C(3')OCH_3), 43.9+ (C2 isomer B), 43.6+ (C2 isomer A), 25.5− (C3 or C4 isomer A), 25.4− (C3 or C4 isomer B), 24.1− (C3 or C4 isomer A), 23.4− (C3 or C4isomer A), 21.4+ (CH_3C=O isomer B), 21.3+ (CH_3C=O isomer A) and 14.0+ (OCH_2CH_3); **MS** (+ESI) *m/z* 319 (M-CH_3CO_2H+H^+, 100 %) and 401 (M+Na^+, 20); **HRMS** (+ESI) Found M+Na^+, 401.1586; $C_{20}H_{26}O_7Na$ requires $M+Na^+$ 401.1576.

3',4',5'-Trimethoxy-2,3,4,5-tetrahydro-[1,1'-biphenyl]-2-carboxylic acid (234)

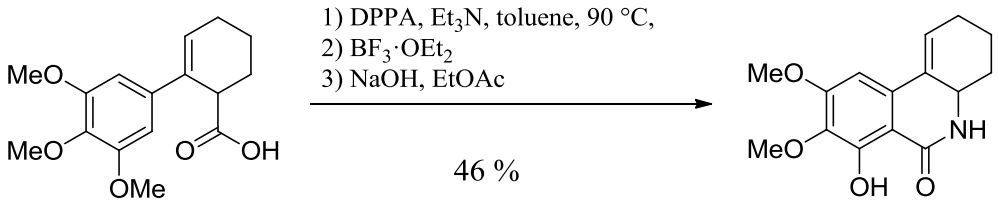


229 **234**

A stirred solution of ester **229** (315 mg, 0.98 mmol) in 1M NaOH/EtOH (1:1 10 mL) was heated at reflux for 6 hrs. The solution was cooled to 0 °C, acidified to pH 2 with 6M HCl and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic fractions were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo* to afford the acid **234** (226 mg, 79 %) as a white solid without further purification

Mp 143-147 °C (from $CHCl_3$); **IR** ν_{max}(thin film) 3161 (OH), 2937, 1073 (C=O), 1582, 1509, 1451, 1414, 1346, 1124 and 1004; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 6.55 (2H, s, C(2')H), 6.20 (1H, dt, *J* 4.0 and 1.0 Hz, C(6)H), 3.84 (6H, s, C(3')OCH_3), 3.83 (3H, s, C(4')OCH_3), 3.68 (1H, t, *J* 4.5 Hz, C(2)H), 2.33-2.18 (2H, m, C(5)H_2), 2.15-2.09 (1H, m, C(3)H_AH_B), 2.06-1.97 (1H, m, C(3)H_AH_B) and 1.83-1.65 (2H, m, C(4)H_2); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 178.8− (CO_2H), 153.1− (C3'), 137.5− (C1'), 137.1− (C4'), 134.1− (C1), 128.6+ (C6), 103.0+ (C2'), 60.8+ (OCH_3), 56.1+ (OCH_3), 42.9+ (C2), 27.0− (C5), 25.5− (C3) and 19.1− (C4); **MS** (+ESI) *m/z* 293 ($M+H^+$, 100 %) and 315 ($M+Na^+$, 20); **HRMS** (+ESI) Found $M+Na^+$, 315.1196; $C_{16}H_{20}O_5Na$ requires $M+Na^+$ 315.1208.

7-Hydroxy-8,9-dimethoxy-3,4,4a,5-tetrahydrophenanthridin-6(2H)-one (236)



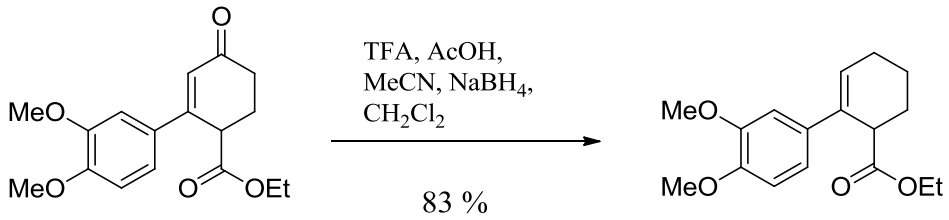
234 **236**

Diphenylphosphoryl azide (81 μL, 0.37 mmol) and Et_3N (51 μL, 0.37 mmol) were added to a stirred suspension of acid **234** (100 mg, 0.34 mmol) in anhydrous toluene (1 mL) at r.t. under Ar. The reaction was heated at 90 °C for 45 mins, then the solvent was removed *in vacuo* and the residue treated with $BF_3{\cdot}OEt_2$ (0.3 mL) and heated at 50 °C under Ar. After 16 hrs, the reaction mixture was quenched with 2M NaOH (5 mL), diluted with EtOAc (2 mL) and heated at 50 °C for 4 hrs. After cooling, the layers were separated and the aqueous fraction further extracted with EtOAc (3 x 15 mL). The combined organic fractions were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo*. After column chromatography [silica, EtOAc-PE gradient from 0:100 to 50:50] the lactam **236** (43 mg, 46 %) was isolated as a white solid.

R_f [EtOAc-PE 4:6] 0.26; **Mp** 202-205 °C (from EtOAc)**; IR** ν_{max}(thin film) 3417, 2935, 1651 (C=O), 1568, 1455, 1376, 1336, 1287, 1255 and 1122; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 12.67 (1H, s, C(7)OH), 6.73 (1H, s, N(5)H), 6.51 (1H, s, C(10)H), 6.20 (1H, ddd, *J* 5.0, 2.5 and 2.5 Hz, C(1)H), 4.30-4.27 (1H, m, C(4a)H), 3.90 (3H, s, C(9)OCH_3), 3.88 (3H, s, C(8)OCH_3), 2.40-2.21 (2H, m, C(2)H_2), 2.16-2.11 (1H, m, C(4)H_AH_B), 1.90-1.87 (1H, m, C(3)H_AH_B) and 1.68-1.59 (2H, m, C(3)H_AH_B and C(4)H_AH_B); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 169.7− (C6=O), 157.2− (C9), 155.5− (C7-OH), 136.3− (C8), 133.7− (C10b), 130.4− (C10a), 125.9+ (C1), 104.3− (C6a), 97.4+ (C10), 60.7+ (C(8)OCH_3), 56.0+ (C(9)OCH_3), 50.7+ (C4a), 29.6− (C4), 25.9− (C2) and 20.0− (C3); **MS** (+ESI) *m/z* 276 ($M+H^+$, 100 %) and 298 ($M+Na^+$, 13); **HRMS** (+ESI) Found $M+Na^+$, 298.1054; $C_{15}H_{27}NO_4Na$ requires $M+Na^+$ 298.1055; **HPLC** t_R 13.0 (97 %).

5.3.3. Successful Synthesis of the Dimethoxy Analogue

Ethyl 3',4'-dimethoxy-2,3,4,5-tetrahydro-[1,1'-biphenyl]-2-carboxylate (237)

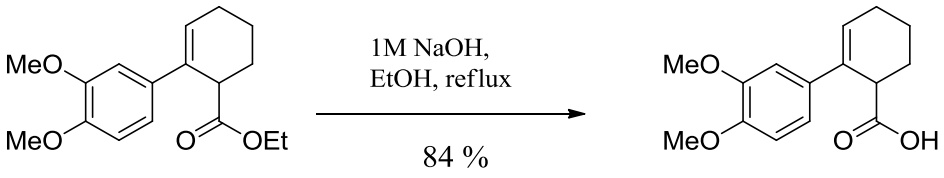


206 **237**

$NaBH_4$ (197 mg, 5.2 mmol) was added portionwise over 3 mins to a stirred solution of TFA (1.2mL), AcOH (1.2 mL) and MeCN (1.2 mL) at 0 °C under Ar. Ketone **206** (304 mg, 1 mmol) in CH_2Cl_2 (6 mL) was added and then the reaction was allowed to warm to r.t. and stirred for 4 hrs. The reaction was neutralised with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo*. After column chromatography [silica, PE-EtOAc gradient from 100:0 to 80:20] the ester product **237** (241 mg, 83 %) was isolated as a colourless oil.

R_f [PE-EtOAc 60:40] 0.57; **IR** ν_{max}(thin film) 2935, 1731 (C=O), 1603, 1582, 1517, 1463, 1252, 1169, 1149, 1028 and 803; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 6.87 (1H, d, *J* 2.0 Hz, C(2')H), 6.84 (1H, dd, *J* 8.5 and 2.0 Hz, C(6')H), 6.77 (1H, d, *J* 8.5 Hz, C(5')H), 6.12 (1H, td, *J* 4.0 and 1.0 Hz, C(6)H), 4.05-3.96 (2H, m, OCH_2CH_3), 3.86 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.66-3.63 (1H, m, C(2)H), 2.32-2.15 (2H, m, $C(5)H_2$), 2.07-1.94 (2H, m, $C(3)H_2$), 1.83-1.73 (1H, m, $C(4)H_AH_B$), 1.69-1.60 (1H, m, $C(4)H_AH_B$) and 1.07 (3H, t, *J* 7.0 Hz, OCH_2CH_3); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 174.7− (C=O), 148.7− (C4'), 148.2− (C3'), 134.8− (C1), 134.5− (C1'), 127.0+ (C6), 117.8+ (C5'), 111.0+ (C6'), 109.3+ (C2'), 60.4− (OCH_2CH_3), 55.9+ (OCH_3), 55.8+ (OCH_3), 43.9+ (C2), 27.1− (C3), 25.5− (C5), 19.4− (C4) and 14.1+ (OCH_2CH_3); **MS** (+ESI) *m/z* 291 ($M+H^+$, 93 %); **HRMS** (+ESI) Found $M+H^+$, 291.1593; $C_{17}H_{23}O_4$ requires $M+H^+$ 291.1596.

3',4'-Dimethoxy-2,3,4,5-tetrahydro-[1,1'-biphenyl]-2-carboxylic acid (238)

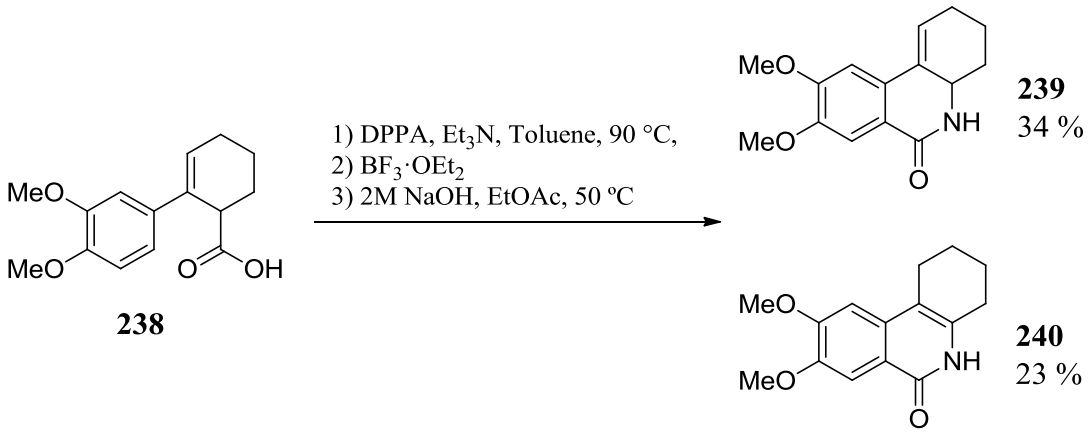


237 **238**

Ester **237** (212 mg, 0.73 mmol) was stirred in refluxing 1M NaOH/EtOH (1:1, 8 mL) for 5 hrs. The solution was then cooled to 0 °C, acidified to pH 2 with 6M HCl and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic fractions were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo* to afford the acid **238** (160 mg, 84 %) as a white solid without further purification.

Mp 102-106 °C (from $CHCl_3$); **IR** ν_{max}(thin film) 2935, 1703 (C=O), 1516, 1463, 1251, 1168, 1145 and 1025; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 6.89 (1H, d, *J* 2.0 Hz, C(5')H), 6.86 (1H, dd, *J* 8.5 and 2.0 Hz, C(6')H), 6.79 (1H, d, *J* 8.5 Hz, C(2')H), 6.17 (1H, td, *J* 4.5 and 1.0 Hz, C(6)H), 3.86 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.69-3.67 (1H, m, C(2)H), 2.33-2.22 (2H, m, C(5)H_2), 2.15-2.01 (1H, m, C(3)H_AH_B), 2.04-1.95 (1H, m, C(3)H_AH_B) and 1.83-1.62 (2H, m, C(4)H_2); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 179.3− (C=O), 148.9− (C4'), 148.3− (C3'), 134.3− (C1), 133.6− (C1'), 127.6+ (C6), 117.6+ (C6'), 111.1+ (C5'), 109.2+ (C2'), 55.9+ (OCH_3), 55.8+ (OCH_3), 42.8+ (C2), 27.0− (C3), 25.5− (C5) and 19.4− (C4); **MS** (+ESI) *m/z* 263 ($M+H^+$, 44 %), 285 ($M+Na^+$, 100); **HRMS** (+ESI) Found $M+H^+$, 263.1284; $C_{15}H_{19}O_4$ requires $M+H^+$ 263.1283.

8,9-Dimethoxy-3,4,4a,5-tetrahydrophenanthridin-6(2H)-one (239) and 8,9-Dimethoxy-1,2,3,4-tetrahydrophenanthridin-6(5H)-one (240)



Diphenylphosphoryl azide (131 μL, 0.61 mmol) was added to a stirred mixture of acid **238** (160mg, 0.61 mmol) and Et_3N (84 μL, 0.61 mmol) in anhydrous toluene (5 mL) at r.t. under Ar. The reaction was heated at 90 °C for 1 hr, then the solvent was removed *in vacuo* and the residue was treated with $BF_3{\cdot}OEt_2$ (1.5 mL) at r.t. under Ar. The mixture was heated at 50 °C for 16 hrs then was quenched with 2M NaOH (15 mL), diluted with EtOAc (10 mL) and heated at 50 °C for 3 hrs. After cooling to r.t., the layers were separated and the aqueous fraction further extracted with EtOAc (3 x 15 mL). The combined organic fractions were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo*. After column chromatography [silica, PE-EtOAc-MeOH gradient from 100:0:0 to 0:100:0 to 0:90:10] the lactam **239** (53 mg, 34 %) was isolated as a white solid and lactam **240** (37 mg, 23 %) as a white solid.

Lactam (239)

R_f [EtOAc] 0.38; **Mp** 250-253 °C (from EtOAc); **IR** ν_{max}(thin film) 3175 (NH), 2905, 2843, 1659 (C=O), 1591, 1555, 1508, 1469, 1456, 1425, 1381, 1277 and 1210; **^{1}H NMR** δ_H(400 MHz, d_6-DMSO) 7.85 (1H, s, N(5)H), 7.37 (1H, s, C(7)H), 7.08 (1H, s, C(10)H), 6.30-6.28 (1H, m, C(1)H), 4.24-4.23 (1H, m, C(4a)H), 3.86 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 2.33-2.26 (1H, m, C(2)H_AH_B), 2.22-2.18 (1H, m, C(2)H_AH_B), 2.13-2.11 (1H, m, C(4)H_AH_B), 1.82-1.76 (1H, m, C(3)H_AH_B) and 1.60-1.46 (2H, m, C(3)H_AH_B and C(4)H_AH_B); **^{13}C NMR** δ_C(100 MHz, d_6-

DMSO) 163.7− (C6=O), 152.0− (C9), 148.5− (C8), 130.7− (C10 a or C10 b), 130.6− (C10a or C10b), 123.8+ (C1), 119.9− (C6a), 109.1+ (C7), 105.5+ (C10), 55.7+ (C(9)O*C*H$_3$), 55.4+ (C(8)O*C*H$_3$), 50.3+ (C4a), 29.2− (C4), 25.2− (C2) and 19.8− (C3); **MS** (+ESI) *m/z* 260 (M+H$^+$, 100 %) and 282 (M+Na$^+$, 33); **HRMS** (+ESI) Found M+H$^+$, 260.1305; $C_{15}H_{18}NO_3$ requires $M+H^+$ 260.1281; **HPLC** t_R 11.4 (98 %).

Lactam (240)

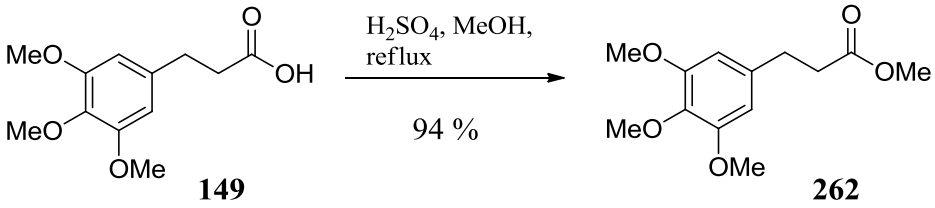
R$_f$ [EtOAc] 0.25; **Mp** sublimes above 255 °C then recrystallises and melts 297-300 °C but with accompanying decomposition (from EtOAc); **IR** ν_{max}(thin film) 3735 (NH), 2918, 1637 (C=O), 1609, 1508, 1266, 1206 and 1021; **^{1}H NMR** δ_H(500 MHz, d$_6$-DMSO) 10.89 (1H, s, N(5)H), 7.58 (1H, s, C(10)H), 6.98 (1H, s, C(7)H), 3.91 (3H, s, C(9)OCH$_3$), 3.85 (3H, s, C(8)OCH$_3$), 2.61 (2H, t, *J* 5.5H, C(1)H$_2$), 2.52-2.49 (2H, m, C(4)H$_2$) and 1.79-1.74 (4H, m, C(2)H$_2$ and C(3)H$_2$); **^{13}C NMR** δ_C(125 MHz, d$_6$-DMSO) 160.8− (C6=O), 152.9− (C9), 147.6− (C8), 134.5− (C4a); 133.3− (C10a), 118.3− (C6a), 107.1+ (C10 and C10b), 102.9+ (C7), 55.6+ (C(9)O*C*H$_3$), 55.4+ (C(8)O*C*H$_3$), 26.4− (C1), 22.8+ (C4), 22.1− (C2 or C3) and 21.6− (C2 or C3); **MS** (+ESI) *m/z* 260 (M+H$^+$, 100 %), 282 (M+Na$^+$, 9) and 519 (2M+Na$^+$, 56); **HRMS** (+ESI) Found M+H$^+$, 260.1324; $C_{15}H_{18}NO_3$ requires $M+H^+$ 260.1281; **HPLC** t_R 11.4 (100 %).

5.4. PRENYLATIONS

General procedure 3: Esterification of carboxylic acids

Following the procedure reported by Bourdron *et al.*,[251] H_2SO_4 (1 drop/mmol) was added to a rapidly stirred solution of carboxylic acid in MeOH (10 mL/mmol) at r.t. The reaction was heated at reflux until the acid had been consumed by TLC. The solvent was then removed *in vacuo*, the residue taken up in saturated aqueous $NaHCO_3$ and extracted with 3 x EtOAc. The combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo* to afford the ester without need for further purification.

Methyl 3-(3',4',5'-trimethoxyphenyl)propanoate (262)

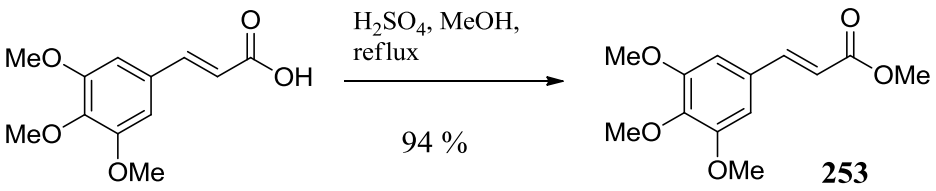


Following general procedure 3, acid **149** (1.20 g, 5 mmol) gave ester **262** (1.20 g, 94 %) as an oil.

IR ν_{max}(thin film) 2947, 2839, 1737 (C=O), 1590, 1508, 1456, 1422, 1240, 1127 and 1009; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 6.41 (2H, s, C(Ar)-H), 3.83 (6H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 2.89 (2H, t, *J* 8.0 Hz, C(3)H_2) and 2.62 (2H, t, *J* 8.0 Hz, C(2)H_2); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 173.2− (C1=O), 153.2− (C(Ar)-O), 136.3− (C(Ar)-O), 105.3+ (C2' and C6'), 60.8+ (ArO*C*H_3), 56.0+ (ArO*C*H_3), 51.6+ (CO_2*C*H_3), 35.8− (C3) and 31.3− (C2).

Spectroscopic data is consistent with reported by Kumar *et al.*[252]

(*E*)-Methyl 3-(3',4',5'-trimethoxyphenyl)acrylate (253)



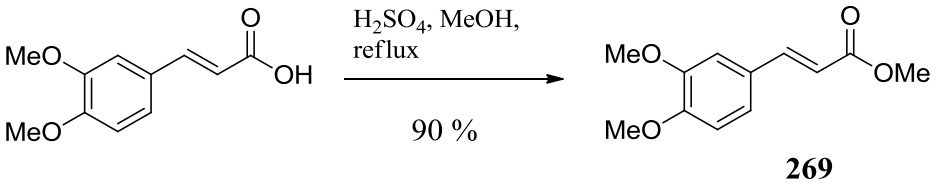
253

Following general procedure 3, the acid (1.19 g, 5 mmol) gave ester **253** (1.18g, 94 %) as a white solid.

R_f [PE-EtOAc 80:20] 0.38; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 7.60 (1H, d, *J* 16.0 Hz, C(3)H), 6.75 (2H, s, C(2')H and C(6')H), 6.34 (1H, d, *J* 16.0 Hz, C(2)H), 3.88 (6H, s, OCH_3), 3.87 (3H, s, OCH_3) and 3.80 (3H, s, OCH_3); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 167.4− (C1=O), 153.4− (Ar), 144.8+ (C3), 140.1− (Ar), 129.9− (Ar), 117.0+ (C2), 105.2+ (C2' and C6'), 60.9+ (OCH_3), 56.1+ (OCH_3) and 51.7+ (OCH_3).

Spectroscopic data is consistent with that reported by Bourdron *et al.*[251]

(*E*)-Methyl 3-(3',4'-dimethoxyphenyl)acrylate (269)



269

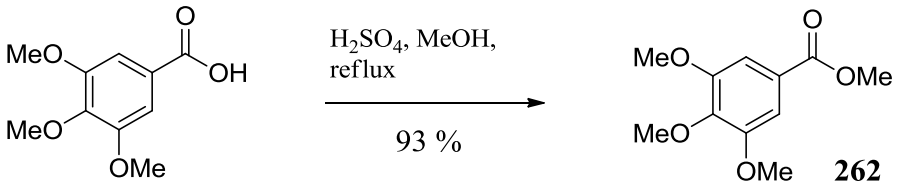
Following general procedure 3, the acid (1.56 g, 7.5 mmol) gave ester **269** (1.50 g, 90 %) as a white solid.

IR ν_{max}(thin film) 2950, 2838, 1712 (C=O), 1636, 1599, 1514, 1464, 1438, 1259, 1196, 1140 and 1024; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 7.66 (1H, d, *J* 16.0 Hz, C(3)H), 7.13 (1H, dd, *J* 8.5 and 2.0 Hz, C(6')H), 7.08 (1H, d, *J* 2.0 Hz, C(2')H), 6.89 (1H, d, *J* 8.5 Hz, C(5')H), 6.34 (1H, d, *J* 16.0 Hz, C(2)H), 3.94 (6H, s, ArOCH_3) and 3.82 (3H, s, CO_2CH_3); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 167.6− (C=O), 151.2− (C(Ar)-O), 149.3− (C(Ar)-O), 144.8+ (C3), 127.4− (C1'), 122.6+ (C(Ar)-H), 115.6−

(C2), 111.1+ (C(Ar)-H), 109.8+ (C(Ar)-H), 56.0+ (ArO*C*H_3), 55.9+ (ArO*C*H_3) and 51.6+ (CO_2*C*H_3).

Spectroscopic data is consistent with that reported by El-Batta *et al.*[253]

Methyl 3,4,5-trimethoxybenzoate (262)



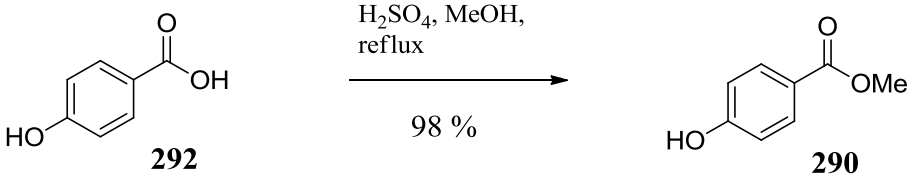
262

Following general procedure 3, the acid (1.06 g, 5 mmol) gave the ester **262** (1.05 g, 93 %) as a white solid.

^{1}H NMR δ_H(400 MHz, $CDCl_3$) 7.30 (2H, s, C(Ar)-H) and 3.90 (12H, s, OCH_3); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 166.7− (C=O), 153.0− (C(Ar)-O), 142.3− (C(Ar)-O), 125.2− (*C*(Ar)-C), 107.0+ (C(Ar)-H), 60.9+ (OCH_3), 56.3+ (OCH_3) and 52.3+ (OCH_3);

Spectroscopic data is consistent with that reported by Elsinghorst *et al.*[254]

Methyl 4-hydroxybenzoate (290)



292 **290**

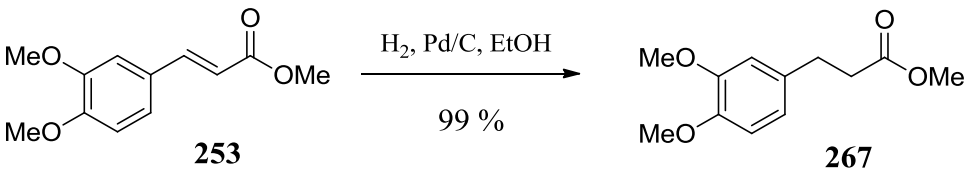
Following general procedure 3, acid **292** (966 mg, 7 mmol) gave ester **290** (1.04 g, 98 %) as a white solid.

IR ν_{max}(thin film) 3253 (OH), 2946, 1687 (C=O), 1608, 1585, 1517, 1438, 1280, 1233, 1171 and 1101; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 7.96 (2H, d, *J* 9.0 Hz, C(Ar)-H), 6.87 (2H, d, *J* 9.0 Hz, C(Ar)-H), 6.03 (1H, s, OH) and 3.89 (3H, s, OCH_3);

^{13}C NMR δ_C(100 MHz, $CDCl_3$) 167.3− (CO_2CH_3), 160.1− (C4-O), 132.0+ (C(Ar)-H), 122.5− (C1), 115.3+ (C(Ar)-H) and 52.0+ (OCH_3).

Spectroscopic data is consistent with that reported by Cuca Suarez *et al.*[255]

Methyl 3-(3',4'-dimethoxyphenyl)propanoate (267)

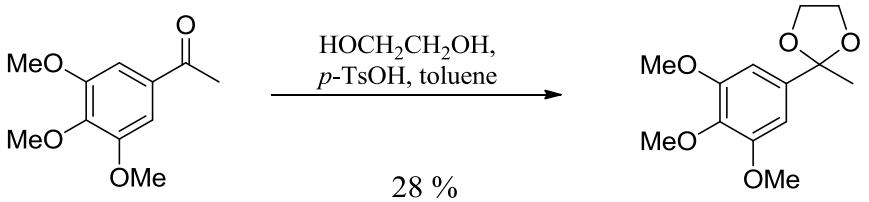


10 % Palladium on carbon (50 mg, 0.05 mmol) was added to a vigorously stirred mixture of methyl 3,4-methylenedioxycinnamate **253** (819 mg, 3.69 mmol) in EtOH (20 mL). After 3 cycles of purging the flask with N_2 then a vacuum, the flask was put under an atmosphere of H_2. After 2 hrs, the mixture was filtered through celite, washing thoroughly with EtOH, then the solvent removed *in vacuo* to afford the methyl propionate **267** (821 mg, 99 %) as a colourless oil without need for further purification.

^{1}H NMR δ_H(400 MHz, $CDCl_3$) 6.84 (1H, d, *J* 8.5 Hz, C(5')-H), 6.77 (1H, dd, *J* 8.5 and 2.0 Hz, C(6')-H), 6.76 (1H, d, *J* 2.0 Hz, C(2')-H), 3.90 (3H, s, $ArOCH_3$), 3.88 (3H, s, $ArOCH_3$), 3.70 (3H, s, CO_2CH_3), 2.93 (2H, t, *J* 7.5 Hz, C(3)H_2), 2.64 (2H, t, *J* 7.5 Hz, C(2)H_2); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 173.4− (C=O), 149.0− (C(Ar)-O), 147.6− (C(Ar)-O), 133.2− (C1'), 120.1+ (C(Ar)-H), 111.8+ (C(Ar)-H), 111.4+ (C(Ar)-H), 56.0+ ($ArOCH_3$), 55.9+ ($ArOCH_3$), 51.6+ (CO_2CH_3), 36.0− (C3) and 30.6− (C2);

Spectroscopic data is consistent with that reported by Moreira *et al.*[256]

2-Methyl-2-(3',4',5'-trimethoxyphenyl)-1,3-dioxolane (277)



261 **277**

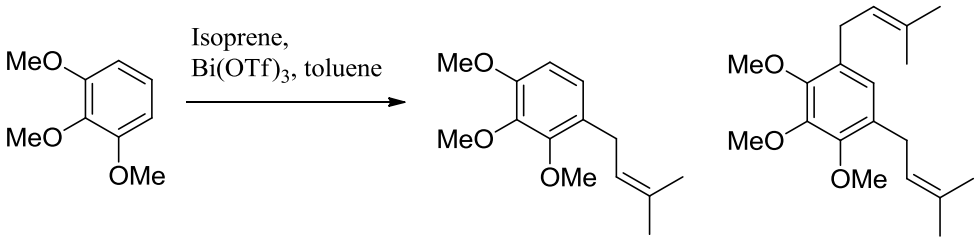
Following a procedure reported by Kong *et al.*,[217] ethylene glycol (2 mL, 36 mmol) and *p*-TsOH.H_2O (190 mg, 1 mmol) in toluene (150 mL) were heated at reflux with azeotropic removal of water using Dean-Stark trap conditions for 1 hr. Acetophenone **261** (1.19 g, 6 mmol) was added in one portion and the reaction heated at reflux for a further 20 hrs. After cooling to r.t., the reaction was washed with saturated aqueous $NaHCO_3$ (2 x 50 mL) and brine (2 x 50 mL), then dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo*. After column chromatography [silica, PE-EtOAc gradient from 100:0 to 75:25] the ketal product **277** (428 mg, 28 %) was isolated as a yellow oil in addition to acetophenone **261** (201 mg, 17 %).

^{1}H NMR δ_H(400 MHz, $CDCl_3$) 6.70 (2H, s, C(2')H and C(6')H), 4.04-4.00 (2H, m, C(4)H_AH_B and C(5)H_AH_B), 3.86 (6H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.82-3.78 (2H, m, C(4)H_AH_B and C(5)H_AH_B) and 1.64 (3H, s, C(2)CH_3); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 153.1− (C(Ar)-O), 139.2− (C1'), 137.6− (C(Ar)-O), 108.8− (C2), 102.4+ (C2' and C6'), 64.5− (C4 and C5), 60.8+ (C(Ar)O*C*H_3), 56.2+ (C(Ar)O*C*H_3) and 27.7+ (C(2)*C*H_3).

General procedure 4: Formation of prenylated and chroman compounds

$Bi(OTf)_3$ (136 mg, 0.2 mmol) was added to a vigorously stirred mixture of substituted aryl (2 mmol) and isoprene (400 µL, 4 mmol) in anhydrous toluene (10 ml) in a thick-walled pressure tube at r.t. under Ar. The flask was sealed and the reaction heated at 40 °C for between 75 mins and 24 hrs then the reaction allowed to cool to r.t.. After column chromatography [silica, PE-Et_2O-EtOAc] the product was isolated.

1,2,3-Trimethoxy-4-(3-methylbut-2-en-1-yl)benzene (256) and 2,3,4-trimethoxy-1,5-bis(3-methylbut-2-en-1-yl)benzene (257)



255 **256** 62 % **257** 20 %

Following general procedure 4, 1,2,3-trimethoxybenzene **255** (336 mg, 2 mmol) gave, after 75 mins at 40 °C and column chromatography [silica, PE-Et_2O gradient from 100 to 90:10], the mono-product **256** (292 mg, 62 %) as a colourless oil and the bis-product **257** (122 mg, 20 %) as a colourless oil.

Mono-product (256)

IR ν_{max}(thin film) 2936, 1599, 1495, 1464, 1416, 1294, 1256, 1096 (C-O) and 1017; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 6.86 (1H, d, *J* 8.5 Hz, C(6)H), 6.64 (1H, d, *J* 8.5 Hz, C(5)H), 5.28 (1H, triplet of septets, *J* 7.5 and 1.5 Hz, $ArCH_2CHC$), 3.91 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.31 (2H, d, *J* 7.5 Hz, $ArCH_2CHC$), 1.77 (3H, s, CCH_3) and 1.77 (3H, s, CCH_3); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 152.0− (C1 or C3), 151.8− (C1 or C3), 142.4− (C2), 132.0− ($ArCH_2CHC$), 127.9− (C4), 123.5+ (C5 or C6), 123.3+ ($ArCH_2CHC$), 107.4+ (C5 or C6), 60.7+ (OCH_3), 60.7+ (OCH_3), 56.0+ (OCH_3), 28.2− ($ArCH_2CHC$), 25.7+ (CCH_3) and 17.7 (CCH_3).

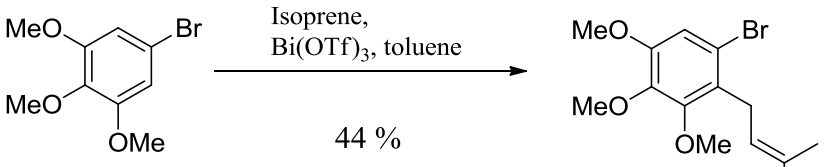
Spectroscopic data is consistent with that of Tarselli *et al.*[257]

Bis-product (257)

IR ν_{max}(thin film) 2965, 2931, 1479, 1460, 1411, 1325, 1235, 1092, 1065 and 1015; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 6.67 (1H, s, C(6)H), 5.25 (2H, triplet of septets, *J* 7.0 and 1.5 Hz, $ArCH_2CHC$), 3.91 (3H, s, OCH_3), 3.83 (6H, s, OCH_3), 3.27 (4H, d, *J* 7.0 Hz, $ArCH_2CHC$) and 1.74 (12H, s, $C(CH_3)_2$); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 149.8− (C2 and C4), 146.3− (C3), 132.0− ($ArCH_2CHC$), 130.3− (C1 and

C5), 124.2+ (C6), 123.3+ (ArCH$_2$*C*HC), 60.8+ (OCH$_3$), 60.6+ (OCH$_3$), 28.4− (Ar*C*H$_2$CHC), 25.7+ (C*C*H$_3$) and 17.8+ (C*C*H$_3$); **MS** (+ESI) *m/z* 305 (M+H$^+$, 9 %); **HRMS** (+ESI) Found M+H$^+$, 305.2103; $C_{19}H_{29}O_3$ requires $M+H^+$ 305.2111.

1-Bromo-3,4,5-trimethoxy-2-(3-methylbut-2-en-1-yl)benzene (259)

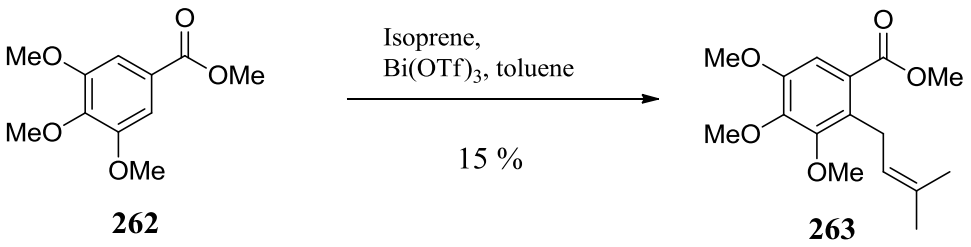


258 **259**

Following general procedure 4, aryl bromide **258** (494 mg, 2 mmol) gave, after 7 hrs at 40 °C and column chromatography [silica, PE-Et$_2$O gradient from 100:0 to 95:5], the product **259** (275 mg, 44 %) as a colourless oil and starting material (246 mg, 50 %).

R$_f$ [PE-Et$_2$O 70:30] 0.63; **IR** ν_{max}(thin film) 2935, 1590, 1482, 1452, 1430, 1396, 1313, 1270, 1237, 1195, 1156, 1113 (C-O), 1045 and 1019; **^{1}H NMR** δ_H(400 MHz, CDCl$_3$) 6.87 (1H, s, C(Ar)H), 5.12 (1H, triplet of septets, *J* 7.0 and 1.5 Hz, ArCH$_2$C*H*C), 3.84, (6H, s, C(3)OCH$_3$ and C(4)OCH$_3$), 3.82 (3H, s, C(5)OCH$_3$), 3.42, (2H, d, *J* 7.0 Hz, ArC*H*$_2$CHC), 1.79 (3H, s, CCH$_3$) and 1.68 (3H, s, CCH$_3$); **^{13}C NMR** δ_C(100 MHz, CDCl$_3$) 152.6− (C3-O), 152.1− (C4-O or C5), 142.0− (C4-O or C5-O), 131.8− (ArCH$_2$CH*C*), 128.1− (C2), 122.1+ (ArCH$_2$*C*HC), 117.9− (C1-Br), 112.0+ (C6), 61.1+ (C(3)OCH$_3$ or C(4)OCH$_3$), 60.7+ (C(3)OCH$_3$ or C(4)OCH$_3$), 56.2+ (C(5)OCH$_3$), 29.3− (Ar*C*H$_2$CHC), 25.7+ (C*C*H$_3$) and 18.1+ (C*C*H$_3$); **MS** (+ESI) *m/z* 315 (M+H$^+$, 97 %), 317 (M+H$^+$, 100) and 337 (M+Na$^+$, 23); **HRMS** (+ESI) Found M+Na$^+$, 337.0400; $C_{14}H_{19}O_3BrNa$ requires $M+Na^+$ 337.0415.

Methyl 3,4,5-trimethoxy-2-(3-methylbut-2-en-1-yl)benzoate (263)

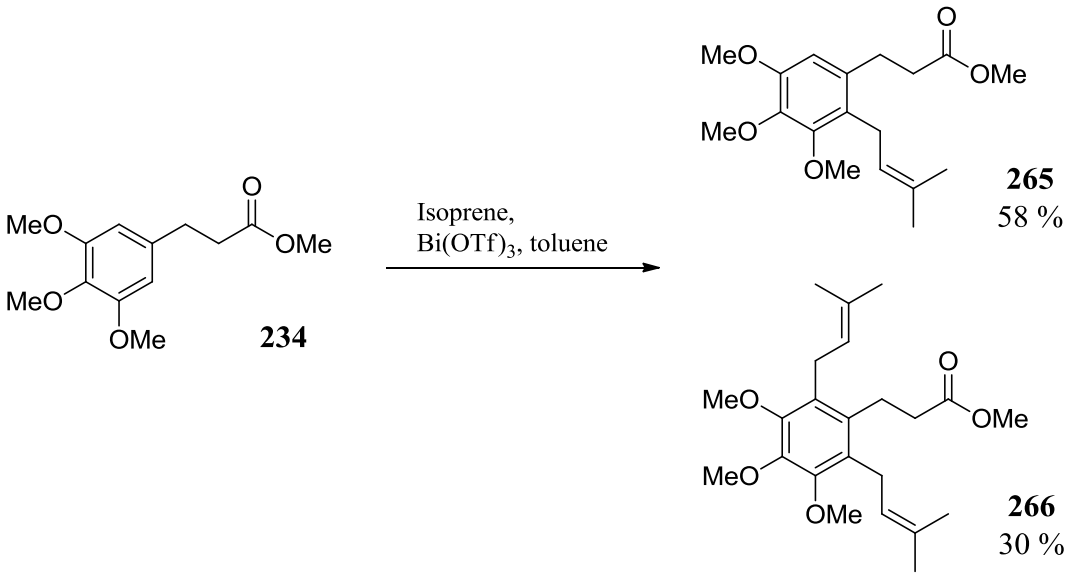


262 **263**

Following general procedure 4, ester **262** (452 mg, 2 mmol) gave, after 5 hrs at 40 °C and column chromatography [silica, PE-Et_2O gradient from 100:0 to 95:5], the product **263** (87 mg, 15 %) as a colourless oil in addition to ester **262** (384 mg, 85 %).

IR ν_{max}(thin film) 2939, 1723 (C=O), 1594, 1491, 1455, 1431, 1401, 1337, 1222, 1154, 1115 and 1055; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 7.17 (1H, s, C(6)H), 5.12 (1H, triplet of septets, *J* 6.5 and 1.5 Hz, $ArCH_2CHC$), 3.91 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.62 (2H, d, *J* 6.5 Hz, $ArCH_2CHC$), 1.75 (3H, d, *J* 0.5 Hz, CCH_3) and 1.66 (3H, d, *J* 1.0 Hz, CCH_3); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 168.0− (C=O), 152.3− (C(Ar)-O), 151.0− (C(Ar)-O), 145.7− (C(Ar)-O), 131.1− ($ArCH_2CHC$), 130.7− (C1), 125.2− (C2), 123.8+ ($ArCH_2CHC$), 109.7+ (C6), 61.0+ (OCH_3), 60.7+ (OCH_3), 56.1+ (OCH_3), 52.0+ (OCH_3), 25.9− ($ArCH_2CHC$), 25.7+ (CCH_3) and 17.9+ (CCH_3); **MS** (+ESI) *m/z* 295 ($M+H^+$, 29 %) and 317 ($M+Na^+$, 12); **HRMS** (+ESI) Found $M+H^+$, 295.1551; $C_{16}H_{23}O_5$ requires $M+H^+$ 295.1545.

Methyl 3-(3',4',5'-trimethoxy-2'-(3-methylbut-2-en-1-yl)phenyl)propanoate (265) and methyl 3-(3',4',5'-trimethoxy-2',6'-bis(3-methylbut-2-en-1-yl)phenyl)propanoate (266)



Following general procedure 4, propionic ester **264** (508 mg, 2 mmol) gave, after 90 mins at 40 °C and column chromatography [silica, PE-Et_2O gradient from 100:0 to 80:20], the mono-product **265** (376 mg, 58 %) as a colourless oil and the bis-product **266** (233 mg, 30 %) as a colourless oil.

Mono-product (265)

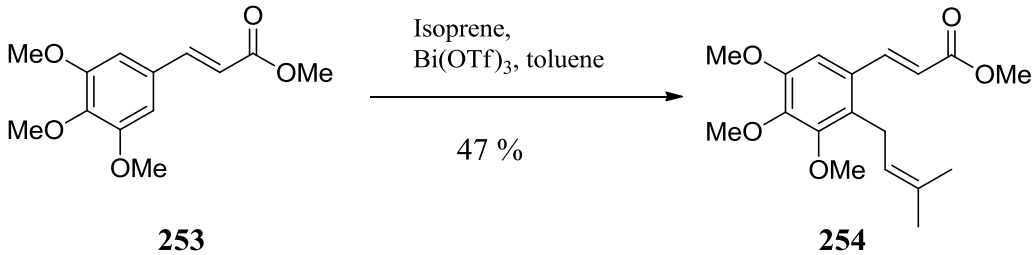
R_f [PE-Et_2O 80:20] 0.27; **IR** ν_{max}(thin film) 2935, 1739 (C=O), 1599, 1578, 1494, 1453, 1406, 1338, 1283, 1239, 1196, 1121, 1073 and 1042; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 6.53 (1H, s, C(6')H), 5.08-5.04 (1H, m, $ArCH_2CHC$), 3.87 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.71 (3H, s, CO_2CH_3), 3.33 (2H, d, *J* 6.5 Hz, $ArCH_2CHC$), 2.93-2.89 (2H, m, $C(3)H_2$) 2.60-2.56 (2H, m, $C(2)H_2$), 1.79 (3H, s, CCH_3) and 1.71 (3H, s, CCH_3); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 173.4− (C1=O), 152.1− (C(Ar)-O), 151.5− (C(Ar)-O), 140.9− (C(Ar)-O), 134.2− (C1' or C2'), 131.1− ($ArCH_2CHC$), 126.2− (C1' or C2'), 123.8+ ($ArCH_2CHC$), 108.4+ (C6'), 60.9+ ($ArOCH_3$), 60.7+ ($ArOCH_3$), 56.0+ ($ArOCH_3$), 51.6+ (CO_2CH_3), 35.5− (C2), 28.3− (C3), 25.6+ (CCH_3), 25.2− ($ArCH_2CHC$) and 17.8+ (CCH_3); **MS** (+ESI)

m/z 345 (M+Na^+, 24 %); **HRMS** (+ESI) Found M+Na^+, 345.1661; $C_{18}H_{20}O_5Na$ requires $M+Na^+$ 345.1672.

Bis-product (266)

R_f [PE-Et_2O 80:20] 0.51; **IR** ν_{max}(thin film) 2948, 2933, 1740 (C=O), 1463, 1416, 1334, 1195, 1170, 1096, 1048 and 982; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 5.10-5.06 (2H, m, $ArCH_2CHC$), 3.91 (3H, s, OCH_3), 3.85 (6H, s, OCH_3), 3.72 (3H, s, CO_2CH_3), 3.36 (4H, d, *J* 6.5 Hz, $ArCH_2CHC$), 2.93-2.89 (2H, m, $C(3)H_2$), 2.50-2.46 (2H, m, $C(2)H_2$), 1.79 (6H, s, CCH_3) and 1.71 (6H, s, CCH_3); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 173.4− (C1=O), 150.3− (C(Ar)-O), 144.8− (C(Ar)-O), 133.0− (C1'), 131.1− ($ArCH_2CHC$), 129.5− (C2' and C5'), 124.0+ ($ArCH_2CHC$), 60.8+ (OCH_3), 60.4+ (OCH_3), 51.5+ (CO_2CH_3), 34.9− (C3), 25.7− ($ArCH_2CHC$), 25.6+ (CCH_3), 24.8− (C2) and 17.8+ (CCH_3); **MS** (+ESI) *m/z* 391 (M+H^+, 20 %); **HRMS** (+ESI) Found M+H^+, 391.2652; $C_{23}H_{35}O_5$ requires $M+H^+$ 391.2479.

(*E*)-Methyl 3-(3',4',5'-trimethoxy-2'-(3-methylbut-2-en-1-yl)phenyl)acrylate (254)



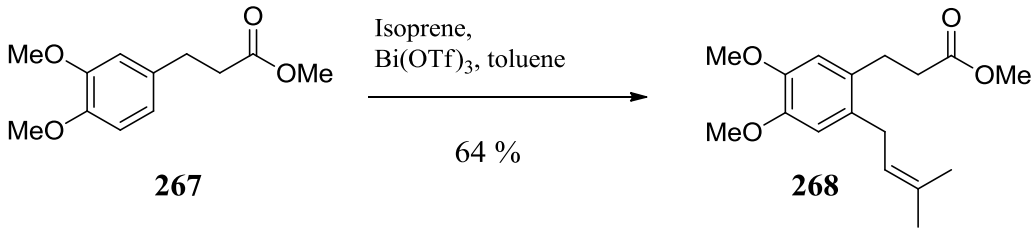
253 **254**

Following general procedure 4, ester **253** (504 mg, 2 mmol) gave, after 4 hrs at 40 °C and column chromatography [silica, PE-Et_2O gradient from 100:0 to 90:10], the mono-product **254** (302 mg, 47 %) as a colourless oil in addition to ester **253** (90 mg, 18 %).

IR ν_{max}(thin film) 2937, 1719 (C=O), 1631, 1592, 1566, 1487, 1409, 1347, 1289, 1254, 1168, 1124; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 7.92 (1H, d, *J* 15.5 Hz, C(3)H), 6.87 (1H, s, C(6')H), 6.26 (1H, d, *J* 15.5 Hz, C(2)H), 5.02 (1H, t, *J* 6.5 Hz, $ArCH_2CHC$), 3.89 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.79 (3H,

s, OCH_3), 3.42 (2H, d, *J* 6.5 Hz, ArCH_2CHC), 1.81 (3H, s, CCH_3) and 1.67 (3H, s, CCH_3); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 167.4− (C=O), 151.9− (C(Ar)-O), 151.7− (C(Ar)-O), 144.2− (C(Ar)-O), 142.6+ (C3), 131.6− (ArCH_2C*H*C), 129.0− (C1' or C2'), 128.6− (C1' or C2'), 123.1+ (ArCH_2*C*HC), 118.0+ (C2), 105.3+ (C6'), 61.0+ (OCH_3), 60.8+ (OCH_3), 55.9+ (OCH_3), 51.6+ (OCH_3), 25.7+ (CCH_3), 25.0− (ArCH_2CHC) and 17.9+ (CCH_3); **MS** (+ESI) *m/z* 343 ($M+Na^+$, 11 %); **HRMS** (+ESI) Found $M+Na^+$, 343.1508; $C_{18}H_{25}O_5$ requires $M+Na^+$ 343.1516.

Methyl 3-(4',5'-dimethoxy-2'-(3-methylbut-2-en-1-yl)phenyl)propanoate (268)

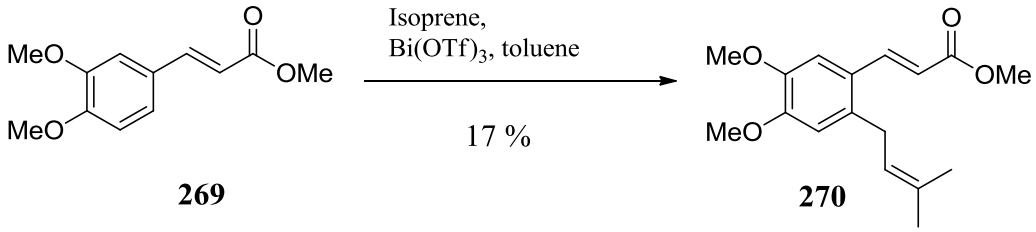


267 **268**

Following general procedure 4, ester **267** (448 mg, 2 mmol) gave, after 6 hrs at 40 °C and column chromatography [silica, PE-Et_2O gradient from 100:0 to 90:10], the mono-product **268** (376 mg, 64 %) as a colourless oil.

R_f [PE-Et_2O 50:50] 0.32; **IR** ν_{max}(thin film) 2934, 2851, 1737 (C=O), 1516, 1458, 1361, 1271, 1209 and 1093; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 6.69 (1H, s, C(3')H or C(6')H), 6.69 (1H, s, C(3')H or C(6')H), 5.21 (1H, triplet of septets, *J* 7.0 and 1.4 Hz, ArCH_2C*H*C), 3.85 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.69 (3H, s, CO_2CH_3), 3.29 (2H, d, *J* 7.0 Hz, ArCH_2CHC), 2.92-2.88 (2H, m, C(3)H_2), 2.59-2.55 (2H, m, C(2)H_2), 1.75 (3H, s, CCH_3) and 1.74 (3H, s, CCH_3); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 173.4− (C1=O), 147.5− (C(Ar)-O), 147.2− (C(Ar)-O), 132.1− (ArCH_2CH*C*), 131.7− (C2'), 130.4− (C1'), 123.4+ (ArCH_2*C*HC), 113.0+ (C3' or C6'), 112.7+ (C3' or C6'), 56.0+ (OCH_3), 55.9+ (OCH_3), 51.5+ (CO_2CH_3), 35.5− (C2), 31.3− (Ar*C*H_2CHC), 27.8− (C3), 25.7+ (CCH_3) and 17.9+ (CCH_3); **MS** (+ESI) *m/z* 293 ($M+H^+$, 15 %) and 315 ($M+Na^+$, 27); **HRMS** (+ESI) Found $M+H^+$, 293.1723; $C_{17}H_{25}O_4$ requires $M+H^+$ 293.1752.

(*E*)-Methyl 3-(4,5-dimethoxy-2-(3-methylbut-2-en-1-yl)phenyl)acrylate (KJ7/23/P) (270)

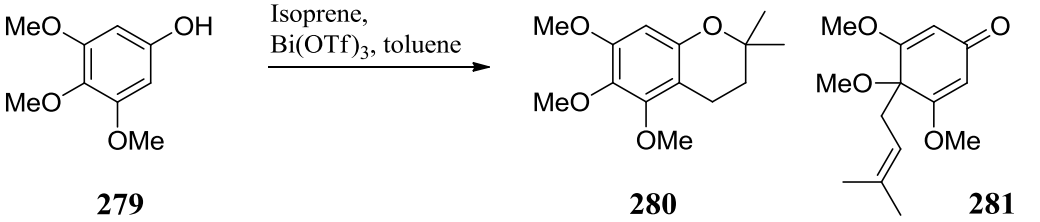


269 **270**

Following general procedure 4, ester **269** (446 mg, 2 mmol) gave, after 6 hrs at 40 °C and column chromatography [silica, PE-Et_2O gradient from 100:0 to 90:10], the mono-product **270** (100 mg, 17 %) as a colourless oil.

IR ν_{max}(thin film) 2934, 1715 (C=O), 1602, 1514, 1458, 1268, 1167 and 1102; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 7.95 (1H, d, *J* 16.0 Hz, C(3)H), 7.05 (1H, s, C(3')H or C(6')H), 6.68 (1H, s, C(3')H or C(6')H), 6.24 (1H, d, *J* 16.0 Hz, C(2)H), 5.16 (1H, triplet of septets, *J* 7.0 and 1.5 Hz, $ArCH_2CHC$), 3.87 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.78 (3H, s, CO_2CH_3), 3.40 (2H, d, *J* 7.0 Hz, $ArCH_2CHC$), 1.76 (3H, s, CCH_3) and 1.71 (3H, s, CCH_3); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 167.7− (C1=O), 151.0− (C(Ar)-O), 147.6− (C(Ar)-O), 142.1+ (C3), 135.5− (C2'), 132.6− ($ArCH_2CHC$), 125.0− (C1'), 122.9+ ($ArCH_2CHC$), 116.3+ (C2), 112.6+ (C3' or C6'), 109.0+ (C3' or C6'), 56.0+ (OCH_3), 55.9+ (OCH_3), 51.5+ (CO_2CH_3), 31.8− ($ArCH_2CHC$), 25.7+ (CCH_3) and 17.9+ (CCH_3); **MS** (+ESI) *m/z* 313 ($M+Na^+$, 9 %); **HRMS** (+ESI) Found $M+Na^+$, 313.142; $C_{17}H_{22}O_4Na$ requires $M+Na^+$ 313.1410.

5,6,7-Trimethoxy-2,2-dimethylchroman (280) and 3,4,5-trimethoxy-4-(3-methylbut-2-en-1-yl)cyclohexa-2,5-dienone (281)



279 **280** 55 % **281** 26 %

Following general procedure 4, acid **279** (368 mg, 2 mmol) gave, after 18 hrs at 40 °C and column chromatography [silica, PE-Et_2O gradient from 100:0 to 85.15 then PE-EtOAc gradient from 50:50 to 30:70], the chroman product **280** (279 mg, 55 %) as an oil and ketone product **281** (132 mg, 26 %) as a white solid.

Chroman (280)

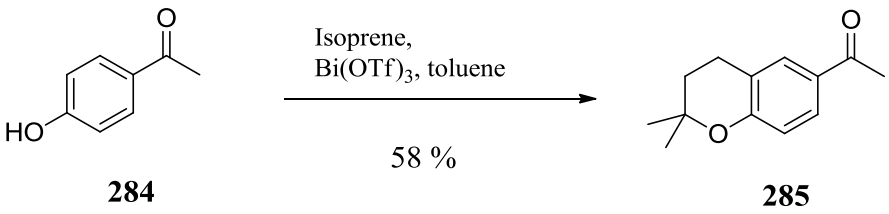
R_f [PE-Et_2O 80:20] 0.52; **IR** ν_{max}(thin film) 2973, 2937, 1611, 1489, 1460, 1413, 1324, 1203, 1158, 1131, 1098, 1045 and 1013; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$ 6.15 (1H, s, C(8)H), 3.87 (3H, s, C(6)OCH_3), 3.79 (3H, s, C(5)OCH_3), 3.78 (3H, s, C(7)OCH_3), 2.63 (2H, t, *J* 7.0 Hz, C(4)H_2), 1.73 (2H, t, *J* 7.0 Hz, C(3)H_2), 1.30 (3H, s, C(2)CH_3) and 1.28 (3H, s, C(2)CH_3); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 152.4− (C7), 151.4− (C5), 150.0− (C8a), 135.4− (C6), 106.7− (C4a), 96.6+ (C8), 74.0− (C2), 61.0+ (C(5)OCH_3), 60.5+ (C(6)OCH_3), 55.8+ (C(7)OCH_3), 32.4− (C3), 26.7+ (C*C*H_3), 26.7+ (C(2)(*C*H_3)$_2$) and 17.0− (C4).

Spectroscopic data was consistent with that reported by Nishikata *et.al.*[258]

Ketone (281)

R_f [PE-EtOAc 40:60] 0.50; **Mp** 106-109 °C (from CH_2Cl_2); **IR** ν_{max}(thin film 2934, 2852, 1659 (C=O), 1625, 1597, 1459, 1374, 1240, 1215, 1163, 1078 and 888; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 5.56 (2H, s, C(2)H and C(5)H), 4.66 (1H, triplet of septets, *J* 7.5 and 1.5 Hz, CH_2CHCMe_2), 3.73 (6H, s, C(3)OCH_3), 3.08 (3H, s, C(4)OCH_3), 2.67 (2H, d, *J* 7.5 Hz, CH_2CHCMe_2), 1.56 (3H, s, CCH_3) and 1.52 (3H, s, CCH_3); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 187.3− (C1=O), 169.4− (C3), 136.3− (C4), 115.7+ (CH_2CHCMe_2), 104.3+ (C2), 79.4− (CH_2CHCMe_2), 56.0+ (C(3)OCH_3), 52.5 (C(4)OCH_3), 35.6− (CH_2CHCMe_2), 25.7+ (C*C*H_3) and 17.6+ (C*C*H_3); **MS** (+ESI) *m/z* 253 ($M+H^+$); **HRMS** (+ESI) Found $M+H^+$, 253.1427; $C_{14}H_{21}O_4$ requires $M+H^+$ 253.1434.

1-(2,2-Dimethylchroman-6-yl)ethanone (285)



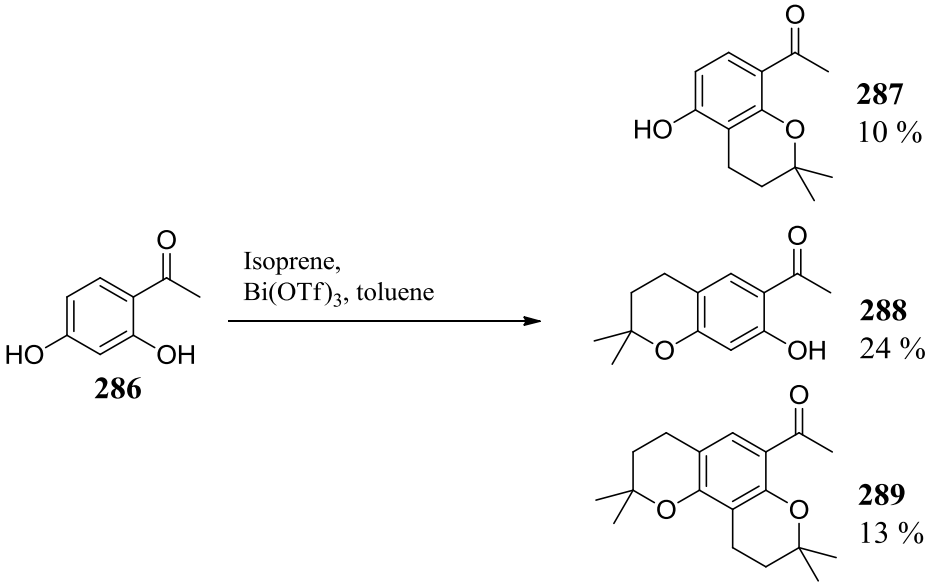
284 **285**

Following general procedure 4, acid **284** (272 mg, 2 mmol) gave, after 18 hrs at 40 °C and column chromatography [silica, PE-Et_2O-EtOAc gradient from 100:0:0 to 85:15:0 then 50:0:50], the product **285** (235 mg, 58 %) as a white solid in addition to phenol **284** (62 mg, 23 %).

R_f [PE-Et_2O 70:30] 0.63; **Mp** 89-93 °C (from CH_2Cl_2); **IR** ν_{max}(thin film) 2976, 1670 (C=O), 1537, 1498, 1419, 1358, 1289, 1265, 1156, 1117; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 7.75 (1H, d, *J* 2.5 Hz, C(5)H), 7.73 (1H, dd, *J* 8.5 and 2.5 Hz, C(7)H), 6.81 (1H, d, *J* 8.5 Hz, C(8)H), 2.83 (2H, t, *J* 6.5 Hz, C(4)H_2), 2.54 (3H, s, CH_3C=O), 1.84 (2H, t, *J* 6.5 Hz, C(3)H_2) and 1.37 (6H, s, C(CH_3)$_2$); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 196.9− (C=O), 158.6− (C8a), 130.5+ (C5), 129.4− (C6), 128.3+ (C7), 120.7− (C4a), 117.2+ (C8), 75.5− (C2), 32.5− (C3), 26.9+ (C(*C*H_3)$_2$), 26.2+ (*C*H_3C=O) and 22.4− (C4).

Spectroscopic data is consistent with that reported by Teng *et al.*[197]

1-(5-Hydroxy-2,2-dimethylchroman-8-yl)ethanone (287), 1-(7-hydroxy-2,2-dimethylchroman-6-yl)ethanone (288), and 1-(2,2,8,8-tetramethyl-2,3,4,8,9,10-hexahydropyrano[2,3-f]chromen-6-yl)ethanone (289)



Following general procedure 4, acid **286** (304 mg, 2 mmol) gave, after 8 hrs at 40 °C and column chromatography [silica, PE-EtOAc gradient from 100:0 to 70:30], the chroman products **287** (46 mg, 10 %) as a white solid, **288** (105 mg, 24 %) as a white solid and **289** (77 mg, 13 %) as an oil.

Chroman (287)

Mp 165-170 °C (from EtOAc); **IR** ν_{max}(thin film) 3172 (OH), 2974, 2931, 1638, 1583 (C=O), 1433, 1362, 1277, 1217, 1157, 1119 and 1051; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 7.68 (1H, d, *J* 8.5 Hz, C(7)H), 7.20 (1H, broad s, OH), 6.47 (1H, d, *J* 8.5 Hz, C(6)H), 2.74 (2H, t, *J* 7.0 Hz, C(4)H_2), 2.64 (3H, s, CH_3C=O), 1.87 (2H, t, *J* 7.0 Hz, C(3)H_2) and 1.43 (6H, s, C(2)(CH_3)$_2$); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 199.7− (C=O), 159.2− (C5), 156.4− (C8a), 129.9+ (C7), 120.3− (C8), 108.5− (C4a), 107.0+ (C6), 75.3− (C2), 32.2+ (*C*H_3C=O), 31.6− (C3), 26.9+ (C(*C*H_3)$_2$) and 17.0− (C4).

Chroman (288)

Mp 115-118 °C (from EtOAc); lit.,[259] 116-117 °C; **IR** ν_{max}(thin film) 2937, 2957, 1867, 1647, 1612, 1495, 1369, 1288, 1280, 1161, 1118, 1058 1020 and 885; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 12.30 (1H, s, OH), 7.41 (1H, s, C(5)H), 6.28 (1H, s, C(8)H), 2.71 (2H, t, *J* 7.0 Hz, C(4)H_2), 2.70 (3H, s, CH_3C=O), 1.80 (2H, t, *J* 7.0Hz, C(3)H_2) and 1.33 (6H, s, C(2)(CH_3)$_2$); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 202.3− (C=O), 162.8− (C7), 161.4− (C8a), 132.2+ (C5), 113.9− (C6), 112.7− (C4a), 104.6+ (C8), 75.9− (C2), 32.7− (C3), 26.4+ (C(2)*C*H_3), 26.1+ (*C*H_3C=O) and 21.7− (C4).

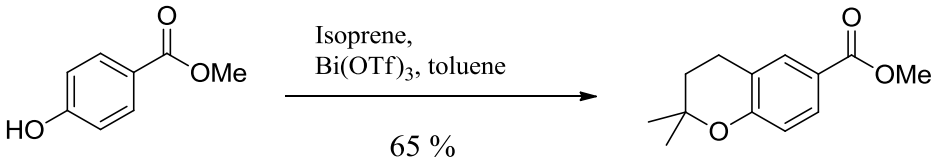
Spectroscopic data was consistent with that reported by Alhuwalia *et al.*259

Chroman (289)

IR ν_{max}(thin film) 2974, 2933, 1662, 1603, 1579, 1457, 1357, 1298, 1258, 1178, 1154, 1120 and 1096; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 7.48 (1H, s, C(5)H), 2.70 (2H, t, *J* 7.0 Hz, C(4)H_2), 2.60 (2H, t, *J* 7.0 Hz, C(10)H_2), 2.56 (3H, s, CH_3C=O), 1.76 (2H, t, *J* 7.0 Hz, C(9)H_2), 1.76 (2H, t, *J* 7.0 Hz, C(3)H_2), 1.35 (6H, s, C(8)(CH_3)$_2$) and 1.32 (6H, s, C(2)(CH_3)$_2$); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 198.6− (C=O), 156.2− (C10b), 153.8− (C6a), 129.2+ (C5), 120.0− (C6), 111.9− (C4a), 109.4− (C10a), 75.3− (C2), 74.7− (C8), 32.8− (C3), 32.3+ (*C*H_3C=O), 31.8− (C9), 27.1+ (C(8)*C*H_3), 26.8+ (C(2)*C*H_3), 21.7− (C4) and 17.2+ (C10).

Spectroscopic data was consistent with that reported by Alhuwalia *et al.*[259]

Methyl 2,2-dimethylchroman-6-carboxylate (291)



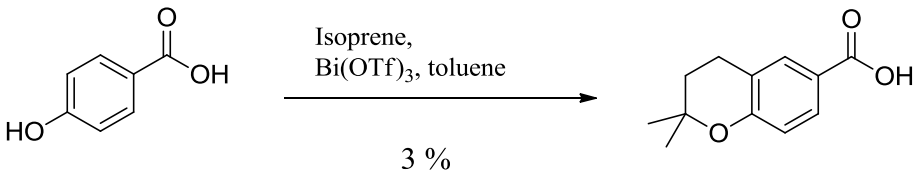
290 **291**

Following general procedure 4, phenol **290** (304 mg, 2 mmol) gave, after 5 hrs at 40 °C and column chromatography [silica, PE-Et_2O gradient from 100:0 to 85:15] afforded the chroman **291** (285 mg, 65 %) as a white solid in addition to phenol **290** (32 mg, 11 %).

R_f [PE-Et_2O 70:30] 0.61; **Mp** 70-74 °C (from CH_2Cl_2); **IR** ν_{max}(thin film) 2975, 2948 (C-H), 1716 (C=O), 1613, 1581, 1493, 1437, 1290, 1263 (C-O), 1155 and 1118; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 7.78 (1H, d, *J* 2.0 Hz, C(5)H), 7.76 (1H, dd, *J* 8.5 and 2.0 Hz, C(7)H), 6.77 (1H, d, *J* 8.5 Hz, C(8)H), 3.86 (3H, s, OCH_3), 2.80 (2H, t, *J* 7.0 Hz, C(4)H_2), 1.82 (2H, t, *J* 7.0 Hz, C(3)H_2) and 1.34 (6H, s, C(2)$(CH_3)_2$); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 167.1− (C=O), 153.3− (C8a), 131.6+ (C5), 129.1+ (C7), 121.5− (C6), 120.6− (C4a), 117.2+ (C8), 75.3− (C2), 51.7+ (OCH_3), 32.6-(C3), 26.9+ (C(CH_3)$_2$) and 22.3− (C4);

Spectroscopic data is consistent with that reported by Batista Jr. *et al.*[260]

2,2-Dimethylchroman-6-carboxylic acid (293)



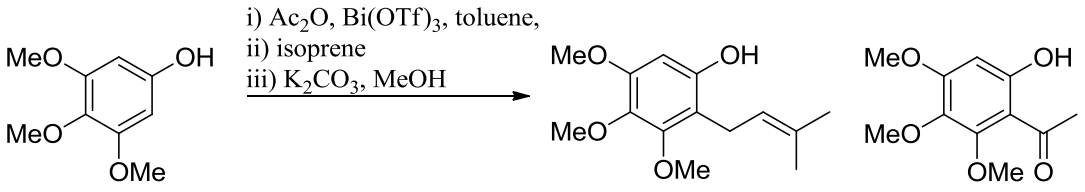
292 **293**

Following general procedure 4, acid **292** (276 mg, 2 mmol) gave, after 24 hrs at 40 °C and column chromatography [silica, PE-EtOAc gradient from 100:0 to 40:60], the product **293** (14 mg, 3 %) as a white solid in addition to phenol **292** (254 mg, 92 %).

IR ν_{max}(thin film) 2975, 1681 (C=O), 1608, 1578, 1443, 1411, 1324, 1296, 1265, 1156 and 1120; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 7.86 (1H, d, *J* 2.0 Hz, C(5)H), 7.84 (1H, dd, *J* 8.5 and 2.0 Hz, C(7)H), 6.82 (1H, d, *J* 8.5 Hz, C(8)H), 2.84 (2H, t, *J* 7.0 Hz, C(4)H_2), 1.84 (2H, t, *J* 7.0 Hz, C(3)H_2) and 1.36 (6H, s, C$(CH_3)_2$); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 172.1− (C=O), 159.1− (C8a), 132.4+ (C5), 129.9+ (C7), 120.8− (C4a or C7), 120.7− (C4a or C7), 117.4+ (C8), 75.6− (C2), 32.5− (C3), 26.9+ (C(CH_3)$_2$) and 22.3− (C4); **MS** (+ESI) *m/z* 207 ($M+H^+$, 100 %) and 229 ($M+Na^+$, 45); **HRMS** (+ESI) Found $M+H^+$, 207.1033; $C_{12}H_{15}O_3$ requires $M+H^+$ 207.1021.

Spectroscopic data is consistent with that reported by Fatope *et al.*[220]

3,4,5-Trimethoxy-2-(3-methylbut-2-en-1-yl)phenol (296) and 1-(6-hydroxy-2,3,4-trimethoxyphenyl)ethanone (297)



279

296
<44 %

297
9 %

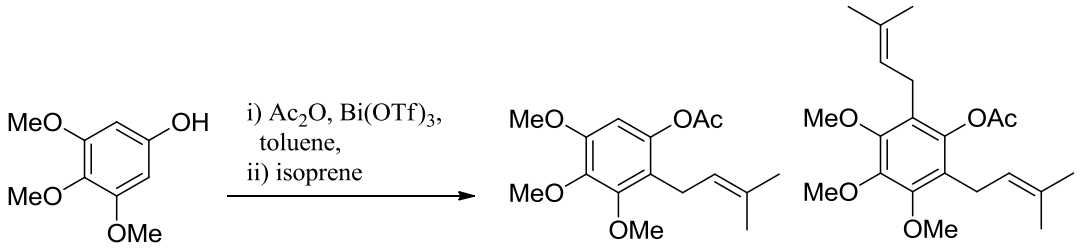
Following a procedure reported by Mohammadpoor-Baltork *et al.*,[224] $Bi(OTf)_3$ (136 mg, 0.2 mmol) then Ac_2O (283 µL, 3 mmol) were added to a stirred suspension of phenol **279** (368 mg, 2 mmol) in anhydrous toluene (10 mL) at r.t. under Ar. After 5 mins, isoprene (400 µL, 4 mmol) was added to the solution, then the flask was sealed and heated at 40 °C for 4 hrs. The solvent was removed and, following a procedure reported by Bates *et al.*,[225] the residue was taken up in MeOH (10 mL) and K_2CO_3 (552 mg, 4 mmol) was added. The reaction was stirred for a 50 mins at r.t. then quenched with saturated aqueous NH_4Cl (30 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic fractions were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo*. Column chromatography [silica, PE-EtOAc gradient from 100:0 to 70:30] afforded the mono-prenylated product **296** (223 mg, <44 %) as a clear oil and the acetophenone product **297** (39 mg, 9 %) as a clear oil.

Acetophenone product 297

^{1}H NMR δ_H(400 MHz, $CDCl_3$) 13.39 (1H, s, C(6)OH), 6.22 (1H, s, C(5)H), 3.97 (3H, s, C(2)OCH_3), 3.87 (3H, s, C(3)OCH_3), 3.76 (3H, s, C(4)OCH_3) and 2.63 (3H, s, CCH_3); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 203.3− (C=O), 161.9− (C6-OH), 160.1− (C3), 155.2− (C2), 134.8− (C4), 108.5− (C1), 96.1+ (C5), 61.0+ (C(2)OCH_3 or C(4)OCH_3), 60.9+ (C(2)OCH_3 or C(4)OCH_3), 56.0+ (C(3)OCH_3) and 31.8+ (CH_3C=O).

Spectroscopic data is consistent with that reported by Combes *et al.*[261]

3,4,5-Trimethoxy-2-(3-methylbut-2-en-1-yl)phenyl acetate (298) and 3,4,5-trimethoxy-2,6-bis(3-methylbut-2-en-1-yl)phenyl acetate (299)



279 **298** 70 % **299** 15 %

Following the procedure reported by Mohammadpoor-Baltork *et al.*,[224] $Bi(OTf)_3$ (136 mg, 0.2 mmol) then Ac_2O (283 µL, 3 mmol) were added to a stirred suspension of phenol (368 mg, 2 mmol) in anhydrous toluene (10 mL) at r.t. under Ar. After 5 mins, isoprene (400 µL, 4 mmol) was added to the solution then the flask was sealed and heated at 40 °C for 1 hr. After column chromatography [silica, PE-Et_2O gradient from 100:0 to 90:10] the mono-prenylated acetate **298** (414 mg, 70 %) was isolated as a clear oil and the bis-prenylated acetate **299** (108 mg, 15 %) as a clear oil.

Mono-product (298)

R_f [PE-Et_2O 80:20] 0.37; **IR** ν_{max}(thin film) 2937, 1767 (C=O), 1608, 1490, 1456, 1408, 1368, 1339, 1206, 1122, 1075 and 1042; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 6.38 (1H, s, C(6)H), 5.06 (1H, triplet of septets, *J* 7.0 and 1.5 Hz, CH_2CHC), 3.85 (3H, s, C(3)OCH_3 or C(4)OCH_3), 3.84 (3H, s, C(3)OCH_3 or C(4)OCH_3), 3.80 (3H, s, C(5)OCH_3), 3.17 (2H, d, *J* 7.0 Hz, CH_2CHC), 2.27 (3H, s, C=OCH_3), 1.73 (3H, s, CCH_3) and 1.66 (3H, d, *J* 1.0 Hz, CCH_3); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 169.5− (C=O), 152.3− (C3), 151.7− (C4), 144.5− (C1), 140.5− (C5), 131.3 ($C(CH_3)_2$), 122.7+ (CH_2CHC), 120.1− (C2), 102.4+ (C6), 61.0+ (C(3)OCH_3 or C(4)OCH_3), 60.8+ (C(3)OCH_3 or C(4)OCH_3), 56.0+ (C(5)OCH_3), 25.6+ (CCH_3), 23.5− (CH_2CHC), 20.8+ (C=OCH_3) and 17.7 (CCH_3); **MS** (+ESI) *m/z* 295 ($M+H^+$, 24 %), 317 ($M+Na^+$, 20); **HRMS** (+ESI) Found $M+H^+$, 239.1533; $C_{16}H_{23}O_5$ requires $M+H^+$ 295.1545.

Bis-product (299)

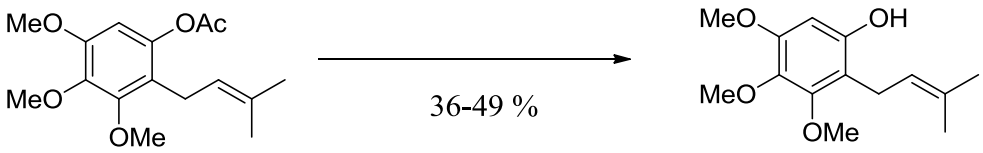
R_f [PE-Et_2O 80:20] 0.61; **IR** ν_{max}(thin film) 2935, 1765 (C=O), 1600, 1463, 1416, 1367, 1346, 1204, 1097,. 1048 and 982; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 5.08 (2H, triplet of septets, *J* 7.0 and 1.5 Hz, CH_2CHC), 3.87 (3H, s, C(4)OCH_3), 3.82 (6H, s, C(3)OCH_3 and C(5)OCH_3), 3.16 (4H, broad s, CH_2CHC), 2.52 (3H, s, C=OCH_3), 1.73 (6H, d, *J* 1.0 Hz, CCH_3) and 1.73 (6H, d, *J* 1.0 Hz, CCH_3); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 169.3− (C=O), 150.3− (C3 and C5), 144.8− (C4), 143.2− (C1), 131.3− ($C(CH_3)_2$), 123.7− (C2 and C5), 122.7+ (CH_2CHC), 61.0+ (C(3)OCH_3 and C(5)OCH_3), 60.6+ (C(4)OCH_3), 25.6+ (CCH_3), 24.1− (CH_2CHC), 20.6+ CH_3C=O) and 17.8+ (CCH_3); **MS** (+ESI) *m/z* 363 ($M+H^+$, 5 %), 385 ($M+Na^+$, 14); **HRMS** (+ESI) Found $M+Na^+$, 385.1975 $C_{21}H_{30}O_5Na$ requires $M+Na^+$ 385.1991.

General Procedure 5: Hydrolysis of phenolic acetates

Method A: Following a procedure reported by Bates *et al.*,[225] K_2CO_3 (2 eq) was added to a solution of the acetate (1 eq) in MeOH (5 mL/mmol) at r.t. and the reaction was stirred for 2 hrs. The suspension was quenched with saturated aqueous NH_4Cl (30 mL) and extracted with EtOAc (3 x 15 mL). The combined organic fractions were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo*. Column chromatography [silica, PE-EtOAc gradient from 100:1 to 75:25] afforded the phenol product.

Method B: Following a procedure reported by Narender *et al.*,[227] NaOAc (10 eq) was added to a solution of the acetate (1 eq) in EtOH/H_2O (10:1, 5.5 mL/mmol) and the reaction heated at reflux for 5 hrs. After cooling, the reaction was diluted with H_2O (15 mL) and extracted with EtOAc (3 x 15 mL). The organic fractions were combined, washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo*. Column chromatography [silica, PE-EtOAc gradient from 100:0 to 75:25] afforded the phenol product.

3,4,5-Trimethoxy-2-(3-methylbut-2-en-1-yl)phenol (296)



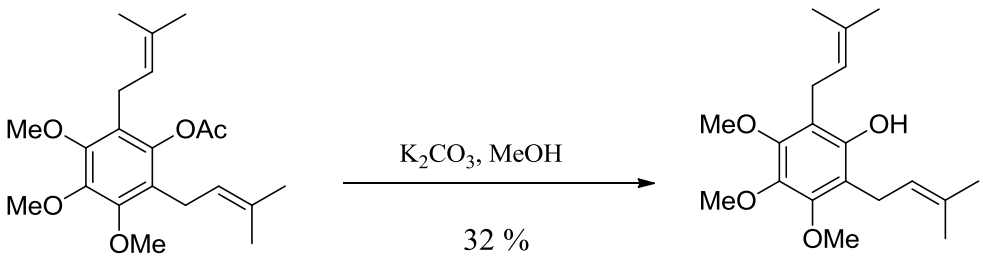
298 **296**

Following general procedure 5A, acetate **298** (411 mg, 1.4 mmol) gave the phenol **296** (173 mg, 49 %) as a yellow amorphous solid. Following general procedure 5B, acetate **298** (132 mg, 0.45 mmol) gave the phenol **296** (41 mg, 36 %), in addition to acetate **298** (53 mg, 40 %).

R_f [PE-EtOAc 75:25] 0.25; **IR** ν_{max}(thin film) 3392 (OH), 2963, 1935, 1607, 1505, 1463, 1415, 1357, 1237, 1197, 1164, 1126, 1082, 1040 and 993; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 6.20 (1H, s, C(6)H), 5.70 (1H, s, C(1)OH), 5.19 (1H, triplet of septets, *J* 7.0 and 1.5 Hz, CH_2CHC), 3.83 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.31 (2H, d, *J* 7.0 Hz, CH_2CHC), 1.78 (3H, d, *J* 1.0 Hz, CCH_3) and 1.70 (3H, d, *J* 1.0 Hz, CCH_3); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 151.9− (C3, C4, or C5), 151.9− (C3, C4, or C5), 150.9− (C1), 136.1− (C3, C4, or C5), 133.6− ($C(CH_3)_2$), 122.6+ (CH_2CHC), 113.0− (C2), 96.6+ (C6), 61.2+ (OCH_3), 61.0+ (OCH_3), 55.9+ (OCH_3), 25.7+ (CCH_3), 22.8− (CH_2CHC) and 17.8+ (CCH_3); **MS** (+ESI) *m/z* 253 ($M+H^+$ 100 %) and 275 ($M+Na^+$, 92); **HRMS** (+ESI) Found $M+Na^+$, 275.1272 $C_{14}H_{20}O_4Na$ requires $M+Na^+$ 275.1259.

Spectroscopic data was consistent with that reported by Parmar *et al.*[222]

3,4,5-Trimethoxy-2,6-bis(3-methylbut-2-en-1-yl)phenol (300)



299 **300**

Following general procedure 5A, acetate **299** (100 mg, 0.27 mmol) gave the phenol **300** (28 mg, 32 %) as an oil.

IR ν_{max}(thin film) 3461 (OH), 2964, 2933, 1605, 1462, 1418, 1357, 1256, 1171, 1097, 1051 and 987; **^{1}H NMR** δ_H(400 MHz, $CDCl_3$) 5.59 (1H, s, C(1)OH), 5.21 (2H, triplet of septets, *J* 7.0 and 1.5 Hz, CH_2CHC), 3.85 (3H, s, C(4)OCH_3), 3.84 (6H, s, C(3)OCH_3 and C(5)OCH_3), 3.34 (4H, d, *J* 7.0 Hz, CH_2CHC), 1.80 (6H, d, *H* 1.0 Hz, CCH_3) and 1.72 (6H, d, H 1.0 Hz, CCH_3); **^{13}C NMR** δ_C(100 MHz, $CDCl_3$) 150.1− (C3 and C5), 149.2− (C1), 140.3− (C4), 133.4− ($C(CH_3)_2$), 122.6+ (CH_2CHC), 116.8− (C2 and C6), 61.1+ (C(3)OCH_3 and C(5)OCH_3), 60.9+ (C(4)OCH_3), 25.8+ (CCH_3), 23.1− (CH_2CHC) and 17.8+ (CCH_3); **MS** (+ESI) *m/z* 321 ($M+H^+$, 50 %); **HRMS** (+ESI) Found $M+H^+$, 321.2066; $C_{19}H_{29}O_4$ requires $M+H^+$ 321.2066.

6. BIBLIOGRAPHY

[11] J. L. Hartwell, *Lloydia*, 1967, **30**, 379-436.

[2] N. Culpeper, *Culpeper's complete herbal consisting of a comprehensive description of nearly all herbs with their medicinal properties and directions for compounding the medicines*, Foulsham.

[3] W. G. van Doorn, *J. Amer. Soc. Hort. Sci.*, 1998, **123**, 146-149.

[4] G. Ceriotti, *Nature*, 1967, **213**, 595-596.

[5] F. Piozzi, C. Fuganti, R. Mondelli and G. Ceriotti, *Tetrahedron*, 1968, **24**, 1119-1131.

[6] T. Okamoto, Y. Torii and Y. Isogai, *Chem. Pharm. Bull.*, 1968, **16**, 1860-1864.

[7] G. Savona, F. Piozzi, M. L. Marino, J. Knight and M. J. Mays, *J. Chem. Soc., Chem. Commun.*, 1970, 1006a-1006a.

[8] A. Immirzi and C. Fuganti, *J. Chem. Soc., Chem. Commun.*, 1972, 240.

[9] F. Piozzi, M. L. Marino, C. Fuganti and A. Di Martino, *Phytochemistry*, 1969, **8**, 1745-1748.

[10] A. Mondon and K. Krohn, *Chem. Ber.*, 1975, **108**, 445-463.

[11] L. Carrasco, M. Fresno and D. Vazquez, *FEBS Lett.*, 1975, **52**, 236-239.

[12] A. Jimenez, L. Sanchez and D. Vazquez, *FEBS Lett.*, 1975, **60**, 66-70; and A. Jimenez, L. Sanchez and D. Vazquez, *FEBS Lett.*, 1975, **55**, 53-56.

[13] P. Dumont, L. Ingrassia, S. Rouzeau, F. Ribaucour, S. Thomas, I. Roland, F. Darro, F. Lefranc and R. Kiss, *Neoplasia*, 2007, **9**, 766-776.

[14] N. A. Thornberry and Y. Lazebnik, *Science*, 1998, **281**, 1312-1316.

[15] D. R. Green and J. Reed, C., *Science*, 1998, **281**, 1309-1312.

[16] I. Petak and J. Houghton, *Pathol. Oncol. Res*, 2001, **7**, 95-106.

[17] A. McLachlan, N. Kekre, J. McNulty and S. Pandey, *Apoptosis*, 2005, **10**, 619-630.

[18] N. Kekre, C. Griffin, J. McNulty and S. Pandey, *Cancer Chemother. Pharmacol.*, 2005, **56**, 29-38.

[19] C. Griffin, C. Hamm, J. McNulty and S. Pandey, *Cancer Cell International*, 2010, **10**, 6.

[20] S. M. Aouad, L. Y. Cohen, E. Sharif-Askari, E. K. Haddad, A. Alam and R.-P. Sekaly, *J. Immunol.*, 2004, **172**, 2316-2323.

[21] L. Ingrassia, F. Lefranc, J. Dewelle, L. Pottier, V. Mathieu, S. Spiegl-Kreinecker, S. Sauvage, Y. M. El, M. Dehoux, W. Berger, Q. E. Van and R. Kiss, *J. Med. Chem.*, 2009, **52**, 1100-1114.

[22] F. Lefranc, S. Sauvage, G. Van Goietsenoven, V. Mégalizzi, D. Lamoral-Theys, O. Debeir, S. Spiegl-Kreinecker, W. Berger, V. Mathieu, C. Decaestecker and R. Kiss, *Mol. Cancer Ther.*, 2009, **8**, 1739-1750.

[23] W. Wang, R. Eddy and J. Condeelis, *Nat. Rev. Cancer*, 2007, **7**, 429-440.

[24] G. R. Pettit, G. R. Pettit, III, R. A. Backhaus, M. R. Boyd and A. W. Meerow, *J. Nat. Prod.*, 1993, **56**, 1682-1687.

[25] U. Rinner, H. L. Hillebrenner, D. R. Adams, T. Hudlicky and G. R. Pettit, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 2911-2915.

[26] U. Rinner, T. Hudlicky, H. Gordon and G. R. Pettit, *Angew. Chem., Int. Ed. Engl.*, 2004, **43**, 5342-5346.

[27] G. R. Pettit, S. A. Eastham, N. Melody, B. Orr, D. L. Herald, J. McGregor, J. C. Knight, D. L. Doubek, G. R. Pettit, III, L. C. Garner and J. A. Bell, *J. Nat. Prod.*, 2006, **69**, 7-13.

[28] S. Ibn-Ahmed, M. Khaldi, F. Chretien and Y. Chapleur, *J. Org. Chem.*, 2004, **69**, 6722-6731.

[29] F. Chrétien, S. I. Ahmed, A. Masion and Y. Chapleur, *Tetrahedron*, 1993, **49**, 7463-7478.

[30] A. S. Kireev, O. N. Nadein, V. J. Agustin, N. E. Bush, A. Evidente, M. Manpadi, M. A. Ogasawara, S. K. Rastogi, S. Rogelj, S. T. Shors and A. Kornienko, *J. Org. Chem.*, 2006, **71**, 5694-5707.

[31] J. McNulty, J. Mao, R. Gibe, R. Mo, S. Wolf, G. R. Pettit, D. L. Herald and M. R. Boyd, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 169-172.

[32] J. McNulty, V. Larichev and S. Pandey, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 5315-5318.

[33] J. Collins, U. Rinner, M. Moser, T. Hudlicky, I. Ghiviriga, A. E. Romero, A. Kornienko, D. Ma, C. Griffin and S. Pandey, *J. Org. Chem.*, 2010, **75**, 3069-3084.

[34] M. Manpadi, A. S. Kireev, I. V. Magedov, J. Altig, P. Tongwa, M. Y. Antipin, A. Evidente, O. W. A. L. van and A. Kornienko, *J. Org. Chem.*, 2009, **74**, 7122-7131.

[35] G. R. Pettit, B. Orr and S. Ducki, *Anti-Cancer Drug Design*, 2000, **15**, 389-395.

[36] G. R. Pettit, N. Melody and D. L. Herald, *J. Nat. Prod.*, 2004, **67**, 322-327.

[37] S. D. Shnyder, P. A. Cooper, N. J. Millington, J. H. Gill and M. C. Bibby, *J. Nat. Prod.*, 2008, **71**, 321-324.

[38] G. R. Pettit, N. Melody and D. L. Herald, *J. Org. Chem.*, 2001, **66**, 2583-2587.

[39] J. H. Rigby and M. E. Mateo, *J. Am. Chem. Soc.*, 1997, **119**, 12655-12656.

[40] D. Gonzalez, T. Martinot and T. Hudlicky, *Tetrahedron Lett.*, 1999, **40**, 3077-3080.

[41] G. E. Keck, T. T. Wager and J. F. D. Rodriquez, *J. Am. Chem. Soc.*, 1999, **121**, 5176-5190.

[42] S. Elango and T.-H. Yan, *J. Org. Chem.*, 2002, **67**, 6954-6959.

[43] T. Curtius, *Chem. Ber.*, 1890, **23**, 3023-3033.

[44] T. Curtius, *J. Prakt. Chem.*, 1894, **50**, 275-294; T. Curtius, *J. Prakt. Chem.*, 1898, **58**, 190-205; T. Curtius, *J. Prakt. Chem.*, 1898, **58**, 205-233; T. Curtius, *Chem. Ber.*, 1902, **35**, 3226-3228; T. Curtius and H. Franzen, *Chem. Ber.*, 1912, **45**, 1037-1044; T. Curtius and W. Giulini, *Chem. Ber.*, 1912, **45**, 1045-1050 and T. Curtius and F. Hartmann, *Chem. Ber.*, 1912, **45**, 1050-1056.

[45] C. A. Buehler and D. E. Pearson, in *Survey of Organic Syntheses*, Wiley-Interscience, New York, 1970, pp. 498-509.

[46] T. Shioiri, in *Comprehensive Organic Chemistry*, eds. B. M. Trost and I. Fleming, Pergammon Press: Oxford, Editon edn., 1991, vol. 6, p. 795.

[47] O. Leogane and H. Lebel, *Synthesis*, 2009, 1935-1940.

[48] P. A. S. Smith, *Org. React. (N.Y.)*, 1946, **3**, 337-449.

[49] M. L. Leathen and E. A. Peterson, *Tetrahedron Lett.*, **51**, 2888-2891.

[50] A. Padwa, K. R. Crawford, P. Rashatasakhon and M. Rose, *J. Org. Chem.*, 2003, **68**, 2609-2617.

[51] P. Bey, F. Gerhart, V. Van Dorsselaer and C. Danzin, *J. Med. Chem.*, 1983, **26**, 1551-1556.

[52] J. Weinstock, *J. Org. Chem.*, 1961, **26**, 3511-3511.

[53] S. Ohta and S. Kimoto, *Chem. Pharm. Bull.*, 1976, **24**, 2969-2976.

[54] T. Shioiri, K. Ninomiya and S. Yamada, *J. Am. Chem. Soc.*, 1972, **94**, 6203-6205.

[55] E. Eibler and J. Sauer, *Tetrahedron Lett.*, 1974, **15**, 2569-2572.

[56] M. S. Newman and H. L. Gildenhorn, *J. Am. Chem. Soc.*, 1948, **70**, 317-319; R. A. Coleman, M. S. Newman and A. B. Garrett, *J. Am. Chem. Soc.*, 1954, **76**, 4534-4538; and Y. Yukawa and Y. Tsuno, *J. Am. Chem. Soc.*, 1959, **81**, 2007-2012.

[57] E. Fahr and L. Neumann, *Angew. Chem., Int. Ed. Engl.*, 1965, **4**, 595-595.

[58] C. R. Hauser and S. W. Kantor, *J. Am. Chem. Soc.*, 1950, **72**, 4284-4285.

[59] G. T. Tisue, S. Linke and W. Lwowski, *J. Am. Chem. Soc.*, 1967, **89**, 6303-6307.

[60] S. Linke, G. T. Tisue and W. Lwowski, *J. Am. Chem. Soc.*, 1967, **89**, 6308-6310.

[61] K. J. Shin, H. R. Moon, C. George and V. E. Marquez, *J. Org. Chem.*, 2000, **65**, 2172-2178.

[62] C. Spino, M.-C. Tremblay and C. Gobdout, *Org. Lett.*, 2004, **6**, 2801-2804.

[63] N. J. Miles, P. G. Sammes, P. D. Kennewell and R. Westwood, *J. Chem. Soc., Perkin Trans. 1*, 1985, 2299-2305; and C. L. Nesloney and J. W. Kelly, *J. Org. Chem.*, 1996, **61**, 3127-3137.

[64] H. Ko, E. Kim, J. E. Park, D. Kim and S. Kim, *J. Org. Chem.*, 2004, **69**, 112-121.

[65] B. M. Trost and S. R. Pulley, *J. Am. Chem. Soc.*, 1995, **117**, 10143-10144.

[66] O. Piccolo, L. Filippini, L. Tinucci, E. Valoti and A. Citterio, *Tetrahedron*, 1986, **42**, 885-891.

[67] S. Hanessian, E. Demont and W. A. L. van Otterlo, *Tetrahedron Lett.*, 2000, **41**, 4999-5003.

[68] K. Afarinkia and A. Ndibwami, *Synlett*, 2007, 1940-1944.

[69] S. Denison and S. T. Hilton, *Synlett*, 2004, 2806-2808.

[70] L. Balázs, M. Nyerges, I. Kádas and L. Tőke, *Synthesis*, 1995, 1373-1375.

[71] W. S. Rapson and R. Robinson, *J. Chem. Soc.*, 1935, 1285-1288.

[72] R. E. Gawley, *Synthesis*, 1976, 777-794.

[73] M. E. Jung, *Tetrahedron*, 1976, **32**, 3-31.

[74] M. D. Turnbull, G. Hatter and D. E. Ledgerwood, *Tetrahedron Lett.*, 1984, **25**, 5449-5452.

[75] H. Watanabe, T. Onoda and T. Kitahara, *Tetrahedron Lett.*, 1999, **40**, 2545-2548.

[76] B. Ganem, *Tetrahedron Lett.*, 1971, **12**, 4105-4108.

[77] R. Iyengar, K. Schildknegt, M. Morton and J. Aubé, *J. Org. Chem.*, 2005, **70**, 10645-10652.

[78] J. D. White, P. Hrnciar and F. Stappenbeck, *J. Org. Chem.*, 1999, **64**, 7871-7884.

[79] F. E. Ziegler and K. J. Hwang, *J. Org. Chem.*, 1983, **48**, 3349-3351.

[80] R. K. Boeckman, M. del Rosario Rico Ferreira, L. H. Mitchell and P. Shao, *J. Am. Chem. Soc.*, 2001, **124**, 190-191.

[81] J. Christoffers and A. Mann, *Chem. Eur. J.*, 2001, **7**, 1014-1027.

[82] C. L. Diedrich, W. Frey and J. Christoffers, *Eur. J. Org. Chem.*, 2007, 4731-4737.

[83] J. d'Angelo, D. Desmaële, F. Dumas and A. Guingant, *Tetrahedron: Asymmetry*, 1992, **3**, 459-505.

[84] H.-J. Liu, T. W. Ly, C.-L. Tai, J.-D. Wu, J.-K. Liang, J.-C. Guo, N.-W. Tseng and K.-S. Shia, *Tetrahedron*, 2003, **59**, 1209-1226.

[85] H. Plieninger and T. Suehiro, *Chem. Ber.*, 1956, **89**, 2789-2794.

[86] A. L. Begbie and B. T. Golding, *J. Chem. Soc., Perkin Trans. 1*, 1972, 602-605.

[87] M. Nour, K. Tan, R. Jankowski and C. Cavé, *Tetrahedron: Asymmetry*, 2001, **12**, 765-769.

[88] E. J. Cragoe, O. W. Woltersdorf, N. P. Gould, A. M. Pietruszkiewicz, C. Ziegler, Y. Sakurai, G. E. Stokker, P. S. Anderson and R. S. Bourke, *J. Med. Chem.*, 1986, **29**, 825-841.

[89] U. Eder, G. Sauer and R. Wiechert, *Angew. Chem., Int. Ed. Engl.*, 1971, **10**, 496-497.

[90] Z. G. Hajos and D. R. Parrish, *J. Org. Chem.*, 1974, **39**, 1615-1621.

[91] P. H.-Y. Cheong, K. N. Houk, J. S. Warrier and S. Hanessian, *Adv. Synth. Catal.*, 2004, **346**, 1111-1115.

[92] E. R. Jarvo and S. J. Miller, *Tetrahedron*, 2002, **58**, 2481-2495.

[93] C. Agami, F. Meynier, C. Puchot, J. Guilhem and C. Pascard, *Tetrahedron*, 1984, **40**, 1031-1038.

[94] J.-I. K. Almstead, T. P. Demuth Jr and B. Ledoussal, *Tetrahedron: Asymmetry*, 1998, **9**, 3179-3183.

[95] F. G. Favaloro, T. Honda, Y. Honda, G. W. Gribble, N. Suh, R. Risingsong and M. B. Sporn, *J. Med. Chem.*, 2002, **45**, 4801-4805.

[96] N. Halland, P. S. Aburel and K. A. Jørgensen, *Angew. Chem.*, 2004, **116**, 1292-1297.

[97] S. G. Davies, A. J. Russell, R. L. Sheppard, A. D. Smith and J. E. Thomson, *Org. Biomol. Chem.*, 2007, **5**, 3190-3200.

[98] T. Bui and C. F. Barbas, *Tetrahedron Lett.*, 2000, **41**, 6951-6954.

[99] D. Rajagopal, R. Narayanan and S. Swaminathan, *Tetrahedron Lett.*, 2001, **42**, 4887-4890.

[100] R. M. Beesley, C. K. Ingold and J. F. Thorpe, *J. Chem. Soc., Trans*, 1915, **107**, 1080-1106.

[101] K. C. Nicolaou, G. Vassilikogiannakis, K. B. Simonsen, P. S. Baran, Y.-L. Zhong, V. P. Vidali, E. N. Pitsinos and E. A. Couladouros, *J. Am. Chem. Soc.*, 2000, **122**, 3071-3079.

[102] K. V. Rao, B. D. Santarsiero, A. D. Mesecar, R. F. Schinazi, B. L. Tekwani and M. T. Hamann, *J. Nat. Prod.*, 2003, **66**, 823-828.

[103] F. Cochard, J. Sapi and J.-Y. Laronze, *Tetrahedron Lett.*, 2001, **42**, 6291-6294.

[104] F. Maertens, A. Van den Bogaert, F. Compernolle and G. Hoornaert, *Eur. J. Org. Chem*, 2004, 4648-4656.

[105] L. G. Hamann, R. I. Higuchi, L. Zhi, J. P. Edwards, X.-N. Wang, K. B. Marschke, J. W. Kong, L. J. Farmer and T. K. Jones, *J. Med. Chem.*, 1998, **41**, 623-639.

[106] L. Keller, S. Beaumont, J.-M. Liu, S. Thoret, J. S. Bignon, J. Wdzieczak-Bakala, P. Dauban and R. H. Dodd, *J. Med. Chem.*, 2008, **51**, 3414-3421.

[107] A. Putey, F. Popowycz, Q.-T. Do, P. Bernard, S. K. Talapatra, F. Kozielski, C. M. Galmarini and B. Joseph, *J. Med. Chem.*, 2009, **52**, 5916-5925.

[108] J. Perregaard, E. K. Moltzen, E. Meier and C. Sanchez, *J. Med. Chem.*, 1995, **38**, 1998-2008.

[109] D. Walker and J. D. Hiebert, *Chem. Rev.*, 1967, **67**, 153-195.

[110] M.-R. Tsai, T.-C. Hung, B.-F. Chen, C.-C. Cheng and N.-C. Chang, *Tetrahedron*, 2004, **60**, 10637-10644.

[111] B. Pohl, T. Luchterhandt and F. Bracher, *Synth. Commun.*, 2007, **37**, 1273 – 1280.

[112] Y. Lingam, D. M. Rao, D. R. Bhowmik and A. Islam, *Synth. Commun.*, 2007, **37**, 4313 - 4318.

[113] S. Mayer, B. Joseph, G. Guillaumet and J.-Y. Mérour, *Synthesis*, 2002, 1871-1878.

[114] Y. Zou, C.-H. Chen, C. D. Taylor, B. M. Foxman and B. B. Snider, *Org. Lett.*, 2007, **9**, 1825-1828.

[115] E. Ciganek, *J. Org. Chem.*, 1995, **60**, 5803-5807.

[116] J. H. Hutchinson, J. J. Cook, K. M. Brashear, M. J. Breslin, J. D. Glass, R. J. Gould, W. Halczenko, M. A. Holahan, R. J. Lynch, G. R. Sitko, M. T. Stranieri and G. D. Hartman, *J. Med. Chem.*, 1996, **39**, 4583-4591.

[117] F. Bracher and D. Hildebrand, *Liebigs Ann. Chem.*, 1992, 1315-1319.

[118] F. Dufour and G. Kirsch, *Synlett*, 2006, 1021-1022.

[119] C. Ito, M. Itoigawa, H. Tokuda, M. Kuchide, H. Nishino and H. Furukawa, *Planta Med.*, 2001, **67**, 473-475.

[120] D. A. Carson, H. B. Cottam and D. B. Wasson, EP 1 193 257 A2, 2002.

[121] J.-P. Wu, J. Wang, A. Abeywardane, D. Andersen, M. Emmanuel, E. Gautschi, D. R. Goldberg, M. A. Kashem, S. Lukas, W. Mao, L. Martin, T. Morwick, N. Moss, C. Pargellis, U. R. Patel, L. Patnaude, G. W. Peet, D. Skow, R. J. Snow, Y. Ward, B. Werneburg and A. White, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 4664-4669.

[122] S. Wang, Y. Dong, X. Wang, X. Hu, J. O. Liu and Y. Hu, *Org. Biomol. Chem.*, 2005, **3**, 911-916.

[123] logP and ClogP calculated using ChemDraw 12.0

[124] C. A. Lipinski, F. Lombardo, B. W. Dominy and P. J. Feeney, *Adv. Drug Delivery Rev.*, 2001, **46**, 3-26.

[125] G. Kohlhagen, K. D. Paull, M. Cushman, P. Nagafuji and Y. Pommier, *Mol. Pharmacol.*, 1998, **54**, 50-58.

[126] T. Ukita, Y. Nakamura, A. Kubo, Y. Yamamoto, Y. Moritani, K. Saruta, T. Higashijima, J. Kotera, M. Takagi, K. Kikkawa and K. Omori, *J. Med. Chem.*, 2001, **44**, 2204-2218.

[127] R. D. Fabio, F. Micheli, G. Alvaro, P. Cavanni, D. Donati, T. Gagliardi, G. Fontana, R. Giovannini, M. Maffeis, A. Mingardi, M. E. Tranquillini and G. Vitulli, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 2254-2259.

[128] M. Tani, T. Aoki, S. Ito, S. Matsumoto, M. Hideshima, K. Fukushima, R. Nozawa, T. Maeda, M. Tashiro, Y. Yokoyama and Y. Murakam, *Chem. Pharm. Bull.*, 1990, **38**, 3261-3267.

[129] Y.-H. Chen, Y.-H. Zhang, H.-J. Zhang, D.-Z. Liu, M. Gu, J.-Y. Li, F. Wu, X.-Z. Zhu, J. Li and F.-J. Nan, *J. Med. Chem.*, 2006, **49**, 1613-1623.

[130] S. Yoshifuji and Y. Arakawa, *Chem. Pharm. Bull.*, 1989, **37**, 3380-3381.

[131] J. C. Arnould, A. Bertrandie, T. G. C. Bird, D. Boucherot, F. Jung, J. J. Lohmann, A. Olivier, J. P. Bailey, W. Bell and G. M. Davies, *J. Med. Chem.*, 1992, **35**, 2631-2642.

[132] J. E. Cragg and R. B. Herbert, *J. Chem. Soc., Perkin Trans. 1*, 1982, 2487-2490.

[133] F. E. Ziegler and M. E. Condon, *J. Org. Chem.*, 1971, **36**, 3707-3714.

[134] B. Umezawa, O. Hoshino, S. Sawaki, H. Sashida, K. Mori, Y. Hamada, K. Kotera and Y. Iitaka, *Tetrahedron*, 1984, **40**, 1783-1790.

[135] M. D. Turnbull, G. Hatter and D. E. Ledgerwood, *Tetrahedron Lett.*, 1984, **25**, 5449-5452.

[136] J. A. Lovett, M. V. Darby and R. E. Counsell, *J. Med. Chem.*, 1984, **27**, 734-740.

[137] D. I. MaGee, M. L. Lee and A. Decken, *J. Org. Chem.*, 1999, **64**, 2549-2554.

[138] [a)] J. A. Bacigaluppo, M. I. Colombo, R. M. Cravero, M. González-Sierra, M. D. Preite, J. Zinczuk and E. A. Rúveda, *Tetrahedron: Asymmetry*, 1994, **5**, 1877-188; and [b)] J. Safaei-Ghomi and Z. Alishahi, *Org. Prep. Proced. Int.*, 2006, **38**, 417 - 422.

[139] S. Kiren and A. Padwa, *J. Org. Chem.*, 2009, **74**, 7781-7789.

[140] M. Banerjee, R. Mukhopadhyay, B. Achari and A. K. Banerjee, *Org. Lett.*, 2003, **5**, 3931-3933.

[141] M. Banerjee, R. Mukhopadhyay, B. Achari and A. K. Banerjee, *Synthesis*, 2006, 1263-1272.

[142] M. Rosenberger and C. Neukom, *J. Org. Chem.*, 1982, **47**, 1779-1782.

[143] T. Oritani, K. Yamashita and C. Kabuto, *J. Org. Chem.*, 1984, **49**, 3689-3694.

[144] A. L. Gemal and J. L. Luche, *J. Am. Chem. Soc.*, 1981, **103**, 5454-5459.

[145] T. Hudlicky, U. Rinner, D. Gonzalez, H. Akgun, S. Schilling, P. Siengalewicz, T. A. Martinot and G. R. Pettit, *J. Org. Chem.*, 2002, **67**, 8726-8743.

[146] P. G. M. Wuts and T. W. Greene, in *Greene's Protecting Groups in Organic Synthesis, Fourth Edition*, Editon edn., 2007, pp. 165-217.

[147] Y. Okumura, A. Ando, R. William Stevens and M. Shimizu, *Tetrahedron*, 2002, **58**, 8729-8736.

[148] G. R. Pettit, S. A. Eastham, N. Melody, B. Orr, D. L. Herald, J. McGregor, J. C. Knight, D. L. Doubek, G. R. Pettit III, L. C. Garner and J. A. Bell, *J. Nat. Prod.*, 2005, **69**, 7-13.

[149] A. Padwa, K. R. Crawford, P. Rashatasakhon and M. Rose, *J. Org. Chem.*, 2003, **68**, 2609-2617.

[150] A. R. Katritzky, K. Widyan and K. Kirichenko, *J. Org. Chem.*, 2007, **72**, 5802-5804.

[151] E. Lieber, R. L. Minnis and C. N. R. Rao, *Chemical Reviews*, 1965, **65**, 377-384.

[152] K. Ninomiya, T. Shioiri and S. Yamada, *Tetrahedron*, 1974, **30**, 2151-2157.

[153] L. Marinescu, J. Thinggaard, I. B. Thomsen and M. Bols, *J. Org. Chem.*, 2003, **68**, 9453-9455.

[154] S.-i. Yamada, K. Ninomiya and T. Shioiri, *Tetrahedron Lett.*, 1973, **14**, 2343-2346.

[155] M. L. Leathen and E. A. Peterson, *Tetrahedron Lett.*, **51**, 2888-2891.

[156] A. S. Cieplak, B. D. Tait and C. R. Johnson, *J. Am. Chem. Soc.*, 1989, **111**, 8447-8462.

[157] A. F. Mateos, E. M. Martín de la Nava and R. R. González, *J. Org. Chem.*, 2001, **66**, 7632-7638.

[158] W.-D. Z. Li and Y.-Q. Wang, *Org. Lett.*, 2003, **5**, 2931-2934.

[159] H. Ohashi, S. Kawai, Y. Sakurai and M. Yasue, *Phytochemistry*, 1992, **31**, 1371-1373.

[160] W. E. Doering, J. Benkhoff and L. Shao, *J. Am. Chem. Soc.*, 1999, **121**, 962-968.

[161] P. G. M. Wuts and T. W. Greene, in *Greene's Protecting Groups in Organic Synthesis, Fourth Edition*, Editon edn., 2007, pp. 448-472.

[162] M. C. Carreño, M. González-López, A. Latorre and A. Urbano, *J. Org. Chem.*, 2006, **71**, 4956-4964.

[163] M. Murakata, Y. Mizuno, H. Yamaguchi and O. Hoshino, *Chem. Pharm. Bull.*, 1999, **47**, 1380-1383.

[164] G. Szántó, L. Hegedus, L. Mattyasovszky, A. Simon, Á. Simon, I. Bitter, G. Tóth, L. Toke and I. Kádas, *Tetrahedron*, 2009, **65**, 8412-8417.

[165] P. G. M. Wuts and T. W. Greene, in *Greene's Protective Groups in Organic Synthesis, Fourth Edition*, 2007, pp. 482-500.

[166] J. C. Craig and S. D. Hurt, *J. Org. Chem.*, 1979, **44**, 1108-1112.

[167] S. Muthusamy, S. A. Babu and C. Gunanathan, *Tetrahedron Lett.*, 2001, **42**, 359-362.

[168] X.-X. Shi and Q.-Q. Wu, *Synth. Commun.*, 2000, **30**, 4081-4086.

[169] Y. Wu, X. Shen, J.-H. Huang, C.-J. Tang, H.-H. Liu and Q. Hu, *Tetrahedron Lett.*, 2002, **43**, 6443-6445.

[170] G. W. Gribble, R. M. Leese and B. E. Evans, *Synthesis*, 1977, 172-175.

[171] M. Beckmann, T. Meyer, F. Schulz and E. Winterfeldt, *Chem. Ber.*, 1994, **127**, 2505-2509.

[172] J. R. Hanson, P. B. Hitchcock, M. D. Liman and S. Nagaratnam, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2183-2187.

[173] M. Di Filippo, I. Izzo, A. Vece, F. De Riccardis and G. Sodano, *Tetrahedron Lett.*, 2001, **42**, 1155-1157.

[174] Z. Freixa, M. M. Pereira, J. C. Bayón, A. M. S. Silva, J. A. R. Salvador, A. M. Beja, J. A. Paixão and M. Ramos, *Tetrahedron: Asymmetry*, 2001, **12**, 1083-1087.

[175] B.-D. Chong, Y.-I. Ji, S.-S. Oh, J.-D. Yang, W. Baik and S. Koo, *J. Org. Chem.*, 1997, **62**, 9323-9325.

[176] T. Akihisa, H. Tokuda, D. Hasegawa, M. Ukiya, Y. Kimura, F. Enjo, T. Suzuki and H. Nishino, *J. Nat. Prod.*, 2006, **69**, 38-42.

[177] M. G. Marcu, A. Chadli, I. Bouhouche, M. Catelli and L. M. Neckers, *J. Biol. Chem.*, 2000, **275**, 37181-37186.

[178] M. K. Hadden, L. Galam, J. E. Gestwicki, R. L. Matts and B. S. J. Blagg, *J. Nat. Prod.*, 2007, **70**, 2014-2018.

[179] [a)] E. Lupinacci, J. Meijerink, J.-P. Vincken, B. Gabriele, H. Gruppen and R. F. Witkamp, *J. Agric. Food Chem.*, 2009, **57**, 7274-7281 and [b)] R. Monteiro, H. Becker, I. Azevedo and C. Calhau, *J. Agric. Food Chem.*, 2006, **54**, 2938-2943.

[180] [a)] R. Nishimura, K. Tabata, M. Arakawa, Y. Ito, Y. Kimura, T. Akihisa, H. Nagai, A. Sakuma, H. Kohno and T. Suzuki, *Biol. Pharm. Bull.*, 2007, **30**, 1878-1883 and [b)] T. Akihisa, H. Tokuda, D. Hasegawa, M. Ukiya, Y. Kimura, F. Enjo, T. Suzuki and H. Nishino, *J. Nat. Prod.*, 2006, **69**, 38-42.

[181] R. J. Rodriguez, C. L. Miranda, J. F. Stevens, M. L. Deinzer and D. R. Buhler, *Food Chem. Toxicol.*, 2001, **39**, 437-445.

[182] C. Hoarau and T. R. R. Pettus, *Synlett*, 2003, 0127-0137.

[183] Y. Asakawa, T. Hashimoto, K. Takikawa, M. Tori and S. Ogawa, *Phytochemistry*, 1991, **30**, 235-251.

[184] G. V. Rao, B. N. Swamy, V. Chandregowda and G. C. Reddy, *Eur. J. Med. Chem.*, 2009, **44**, 2239-224.

[185] D. Leonori and I. Coldham, *Adv. Synth. Catal.*, 2009, **351**, 2619-2623.

[186] [a)] S. Gester, P. Metz, O. Zierau and G. Vollmer, *Tetrahedron*, 2001, **57**, 1015-1018; [b)] K. Sugamoto, C. Kurogi, Y.-i. Matsushita and T. Matsui, *Tetrahedron Lett.*, 2008, **49**, 6639-6641 and [c)] Y. L. Jin, S. Kim, Y. S. Kim, S.-A. Kim and H. S. Kim, *Tetrahedron Lett.*, 2008, **49**, 6835-6837.

[187] J. M. Hastings, M. K. Hadden and B. S. J. Blagg, *J. Org. Chem.*, 2007, **73**, 369-373 and S. Tischer and P. Metz, *Adv. Synth. Catal.*, 2007, **349**, 147-151.

[188] F. Bigi, S. Carloni, R. Maggi, C. Muchetti, M. Rastelli and G. Sartori, *Synthesis*, 1998, 301-304.

[189] D. N. Sarma, P. Baruah, U. C. Pandey and R. P. Sharma, *Tetrahedron Lett.*, 1984, **25**, 5581-5584.

[190] L. F. Fieser, W. P. Campbell, E. M. Fry and M. D. Gates, *J. Am. Chem. Soc.*, 1939, **61**, 3216-3223.

[191] G. W. Burton and K. U. Ingold, *Ann. N. Y. Acad. Sci.*, 1989, **570**, 7-22.

[192] F. Zelefack, D. Guilet, N. Fabre, C. Bayet, S. Chevalley, S. Ngouela, B. N. Lenta, A. Valentin, E. Tsamo and M.-G. Dijoux-Franca, *J. Nat. Prod.*, 2009, **72**, 954-957.

[193] S. Prado, Y. L. Janin, B. Saint-Joanis, P. Brodin, S. Michel, M. Koch, S. T. Cole, F. Tillequin and P.-E. Bost, *Bioorg. Med. Chem.*, 2007, **15**, 2177-2186.

[194] T. Akihisa, H. Tokuda, D. Hasegawa, M. Ukiya, Y. Kimura, F. Enjo, T. Suzuki and H. Nishino, *J. Nat. Prod.*, 2006, **69**, 38-42.

[195] B. T. Ngadjui, B. M. Abegaz, E. Dongo, H. Tamboue and K. Fogue, *Phytochemistry*, 1998, **48**, 349-354.

[196] D. Bernier and R. Brückner, *Synthesis*, 2007, 2249-2272.

[197] M. Teng, T. T. Duong, A. T. Johnson, E. S. Klein, L. Wang, B. Khalifa and R. A. S. Chandraratna, *J. Med. Chem.*, 1997, **40**, 2445-2451.

[198] L. Claisen, *Ber. Dtsch. Chem. Ges. B*, 1921, **54B**, 200-203.

[199] A. R. Bader and W. C. Bean, *J. Am. Chem. Soc.*, 1958, **80**, 3073-3076.

[200] K. C. Dewhirst and F. F. Rust, *J. Org. Chem.*, 1963, **28**, 798-802.

[201] V. K. Ahluwalia and K. K. Arora, *Tetrahedron*, 1981, **37**, 1437-1439.

[202] M. R. Dintzner, K. M. McClelland, K. M. Morse and M. H. Akroush, *Synlett*, 2004, 2028-2030.

[203] S. W. Youn, *Synlett*, 2007, 3050-3054.

[204] L. A. Adrio and K. K. Hii, *Chem. Commun.*, 2008, 2325-2327.

[205] T. Narender, K. P. Reddy and Shweta, *Synth. Commun.*, 2009, **39**, 384-394.

[206] H. Gaspard-Iloughmane and R. C. Le, *Eur. J. Org. Chem.*, 2004, 2517-2532.

[207] S. Antoniotti, *Synlett*, 2003, 1566-1567.

[208] A. Orita, C. Tanahashi, A. Kakuda and J. Otera, *Angew. Chem., Int. Ed. Engl.*, 2000, **39**, 2877-2879.

[209] F. H. A. Kwie, C. Baudoin-Dehoux, C. Blonski and C. Lherbet, *Synth. Commun.*, 2010, **40**, 1082-1087.

[210] B. Bouguerne, P. Hoffmann and C. Lherbet, *Synth. Commun.*, 2010, **40**, 915-926.

[211] B. Sreedhar, V. Swapna and C. Sridhar, *Synth. Commun.*, 2004, **34**, 1433-1440.

[212] T. Ollevier and E. Nadeau, *J. Org. Chem.*, 2004, **69**, 9292-9295.

[213] T. Ollevier and E. Nadeau, *Org. Biomol. Chem.*, 2007, **5**, 3126-3134.

[214] T. Ollevier, V. Desyroy and E. Nadeau, *Arkivoc*, 2007, 10-20.

[215] R. Dumeunier and I. E. Markó, *Tetrahedron Lett.*, 2004, **45**, 825-829.

[216] M. D. Carrigan, D. Sarapa, R. C. Smith, L. C. Wieland and R. S. Mohan, *J. Org. Chem.*, 2002, **67**, 1027-1030.

[217] Y. Kong, K. Wang, M. C. Edler, E. Hamel, S. L. Mooberry, M. A. Paige and M. L. Brown, *Bioorg. Med. Chem.*, **18**, 971-977.

[218] [a)] Y. Inamori, K. Baba, H. Tsujibo, M. Taniguchi, K. Nakata and M. Kozawa, *Chem. Pharm. Bull.*, 1991, **39**, 1604-1605; [b)] K. Sugamoto, C. Kurogi, Y.-i.

Matsushita and T. Matsui, *Tetrahedron Lett.*, 2008, **49**, 6639-6641; and [c)] E. Lupinacci, J. Meijerink, J.-P. Vincken, B. Gabriele, H. Gruppen and R. F. Witkamp, *J. Agric. Food Chem.*, 2009, **57**, 7274-7281.

[219] X.-W. Yang, J.-S. Wang, Y.-H. Wang, H.-T. Xiao, X.-J. Hu, S.-Z. Mu, Y.-L. Ma, H. Lin, H.-P. He, L. Li and X.-J. Hao, *Planta Med.*, 2007, **73**, 496,498.

[220] M. O. Fatope and D. J. Abraham, *J. Med. Chem.*, 1987, **30**, 1973-1977.

[221] S. Jensen, C. E. Olsen, O. Dutt Tyagi, P. M. Boll, F. A. Hussaini, S. Gupta, K. S. Bisht and V. S. Parmar, *Phytochemistry*, 1994, **36**, 789-792.

[222] V. S. Parmar, S. Gupta, K. S. Bisht, S. Mukherjee, P. M. Boll and W. Errington, *Acta Chem. Scand.*, 1996, **50**, 558-560.

[223] S. Mukherjee, V. Kumar, A. K. Prasad, H. G. Raj, M. E. Bracke, C. E. Olsen, S. C. Jain and V. S. Parmar, *Bioorg. Med. Chem.*, 2001, **9**, 337-345.

[224] I. Mohammadpoor-Baltork, H. Aliyan and A. Reza Khosropour, *Tetrahedron*, 2001, **57**, 5851-5854.

[225] R. W. Bates, C. J. Gabel, J. Ji and T. Rama-Devi, *Tetrahedron*, 1995, **51**, 8199-8212.

[226] B. Sreedhar, V. Swapna and C. Sridhar, *Synth. Commun.*, 2004, **34**, 1433-1440.

[227] T. Narender, K. P. Reddy and G. Madhur, *Synth. Commun.*, 2009, **39**, 1949-1956.

[228] D. K. Winter, A. Drouin, J. Lessard and C. Spino, *J. Org. Chem.*, **75**, 2610-2618.

[229] J. A. Nieman, J. E. Coleman, D. J. Wallace, E. Piers, L. Y. Lim, M. Roberge and R. J. Andersen, *J. Nat. Prod.*, 2002, **66**, 183-199.

[230] D. Ben-Ishai, Z. Inbal and A. Warshawsky, *J. Heterocycl. Chem.*, 2009, **7**, 615-620.

[231] Y. Haga, M. Okazaki and Y. Shuto, *Biosci., Biotechnol., Biochem.*, 2003, **67**, 2183-2193.

[232] M. Hanaoka, C. Mukai, I. Hamanaka, K. Seki and Y. Arata, *Chem. Pharm. Bull.*, 1982, **30**, 2793-2796.

[233] L. M. Mohunta and J. N. Ray, *J. Chem. Soc.*, 1934, 1263-1264.

[234] M. Bois-Choussy, M. De Paolis and J. Zhu, *Tetrahedron Lett.*, 2001, **42**, 3427-3430.

[235] R. H. F. Manske and H. L. Holmes, *J. Am. Chem. Soc.*, 1945, **67**, 95-98.

[236] R. A. Abramovitch and D. Shapiro, *J. Chem. Soc.*, 1956, 4589-4592.

[237] S. V. Luis and M. I. Burguete, *Tetrahedron*, 1991, **47**, 1737-1744.

[238] K. V. Rao, B. D. Santarsiero, A. D. Mesecar, R. F. Schinazi, B. L. Tekwani and M. T. Hamann, *J. Nat. Prod.*, 2003, **66**, 823-828.

[239] R. W. Jackson and R. H. Manske, *J. Am. Chem. Soc.*, 1930, **52**, 5029-5035.

[240] A. J. Thakur, A. Boruah, D. Prajapati and J. S. Sandhu, *Synth. Commun.*, 2000, **30**, 2105-2111.

[241] A. S. Bailey and M. H. Vandrevala, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1512-1515.

[242] C. Xie, N. C. Veitch, P. J. Houghton and M. S. J. Simmonds, *Phytochemistry*, 2004, **65**, 3041-3047.

[243] Y. Kondo, J. Imai and H. Inoue, *J. Chem. Soc., Perkin Trans. 1*, 1980, 911-918.

[244] T. Sakamoto, N. Miura, Y. Kondo and H. Yamanaka, *Chem. Pharm. Bull.*, 1986, **34**, 2760-2765.

[245] A. Chatterjee, S. Bose and C. Ghosh, *Tetrahedron*, 1959, **7**, 257-261.

[246] A. Tahri, K. J. Buysens, E. V. Van der Eycken, D. M. Vandenberghe and G. J. Hoornaert, *Tetrahedron*, 1998, **54**, 13211-13226.

[247] J. R. Johnson, A. A. Larsen, A. D. Holley and K. Gerzon, *J. Am. Chem. Soc.*, 1947, **69**, 2364-2370.

[248] J.-C. Jung and O.-S. Park, *Synth. Commun.*, 2007, **37**, 1665-1673.

[249] K. Asahina, *Chem. Ber.*, 1936, **69**, 450-452.

[250] N. J. Lawrence, R. P. Patterson, L.-L. Ooi, D. Cook and S. Ducki, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 5844-5848.

[251] J. Bourdron, L. Commeiras, P. Barbier, V. Bourgarel-Rey, E. Pasquier, N. Vanthuyne, J.-C. Hubaud, V. Peyrot and J.-L. Parrain, *Bioorg. Med. Chem.*, 2006, **14**, 5540-5548.

[252] V. Kumar, A. Sharma and A. Sinha, *Helv. Chim. Acta*, 2006, **89**, 483-495.

[253] A. El-Batta, C. Jiang, W. Zhao, R. Anness, A. L. Cooksy and M. Bergdahl, *J. Org. Chem.*, 2007, **72**, 5244-5259.

[254] P. W. Elsinghorst, C. M. González Tanarro and M. Gütschow, *J. Med. Chem.*, 2006, **49**, 7540-7544.

[255] L. E. Cuca Suarez, M. E. Pattarroyo, J. M. Lozano and F. Delle Monache, *Nat. Prod. Res.*, 2009, **23**, 370-374.

[256] D. d. L. Moreira, E. F. Guimarães and M. A. C. Kaplan, *Phytochemistry*, 2000, **55**, 783-786.

[257] M. A. Tarselli, A. Liu and M. R. Gagné, *Tetrahedron*, 2009, **65**, 1785-1789.

[258] T. Nishikata, Y. Kobayashi, K. Kobayshi, Y. Yamamoto and N. Miyaura, *Synlett*, 2007, 3055-3057.

[259] Q. Wang, X. She, X. Ren, J. Ma and X. Pan, *Tetrahedron: Asymmetry*, 2004, **15**, 29-34.

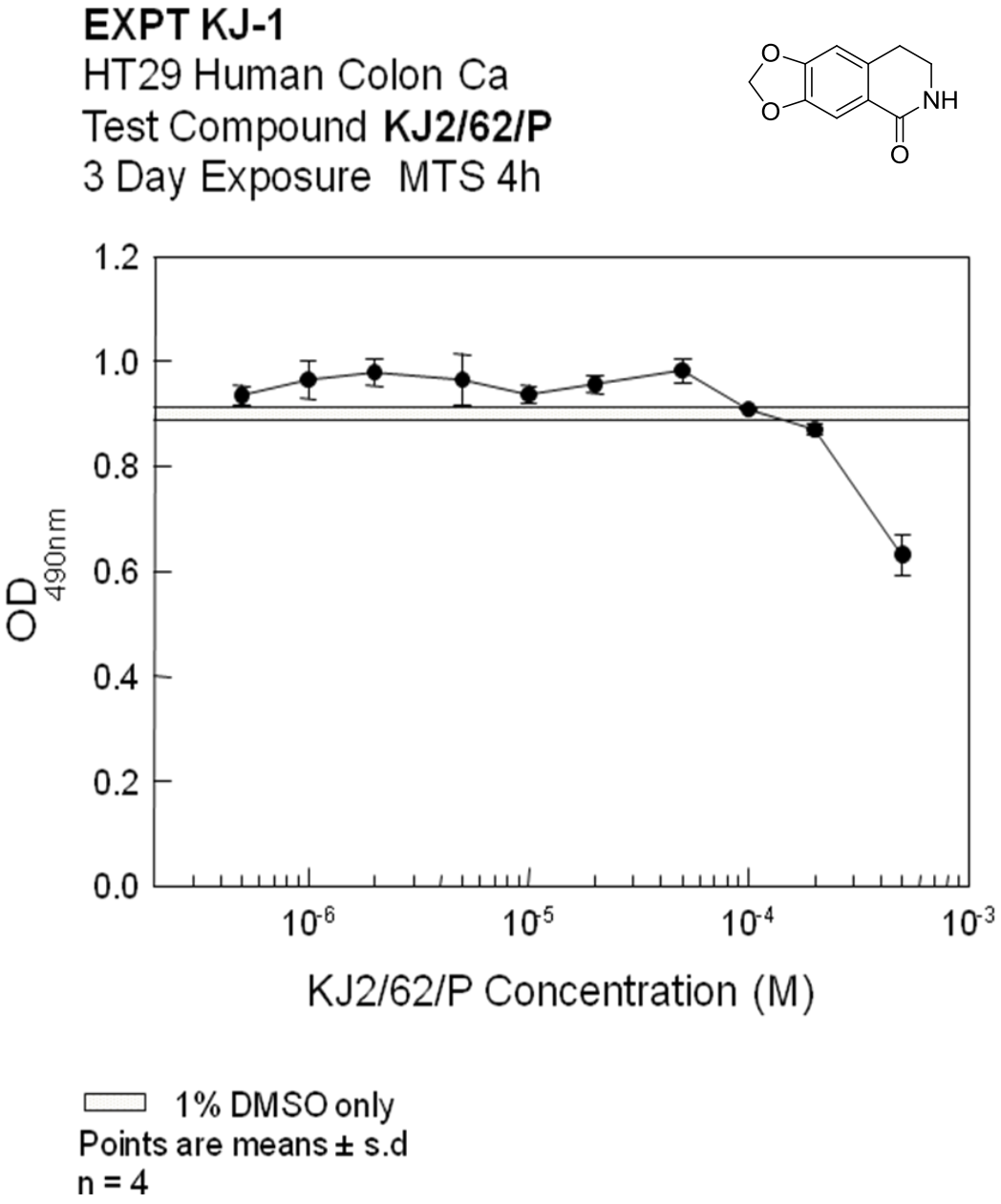
[260] J. M. Batista Jr., A. A. Lopes, D. L. Ambrósio, L. O. Regasini, M. J. Kato, V. d. S. Bolzani, R. M. B. Cicarelli and M. Furlan, *Biol. Pharm. Bull.*, 2008, **31**, 538-540.

[261] S. Combes, J.-P. Finet and D. Siri, *J. Chem. Soc., Perkin Trans. 1*, 2002, 38-44.

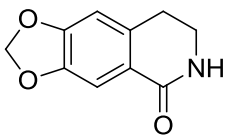
7. APPENDICES

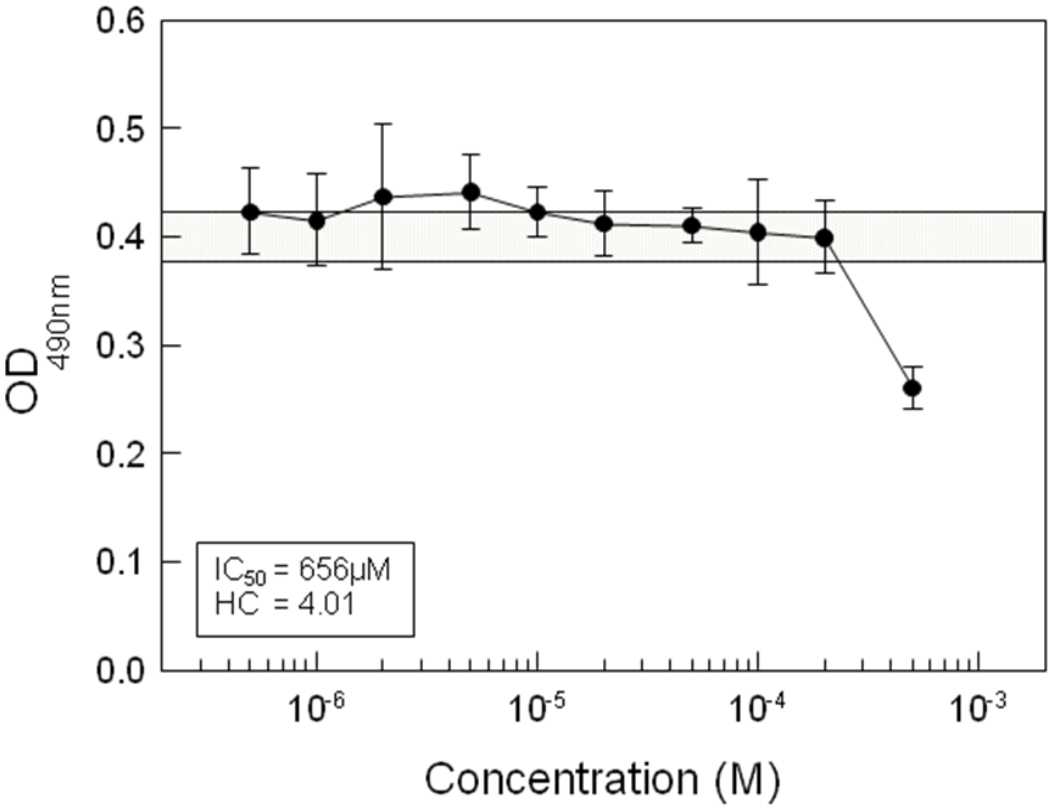
7.1. APPENDIX 1: BIOLOGICAL DATA

7,8-Dihydro-6H-[1,3]dioxolo[4,5-g]isoquinolin-5-one (144)



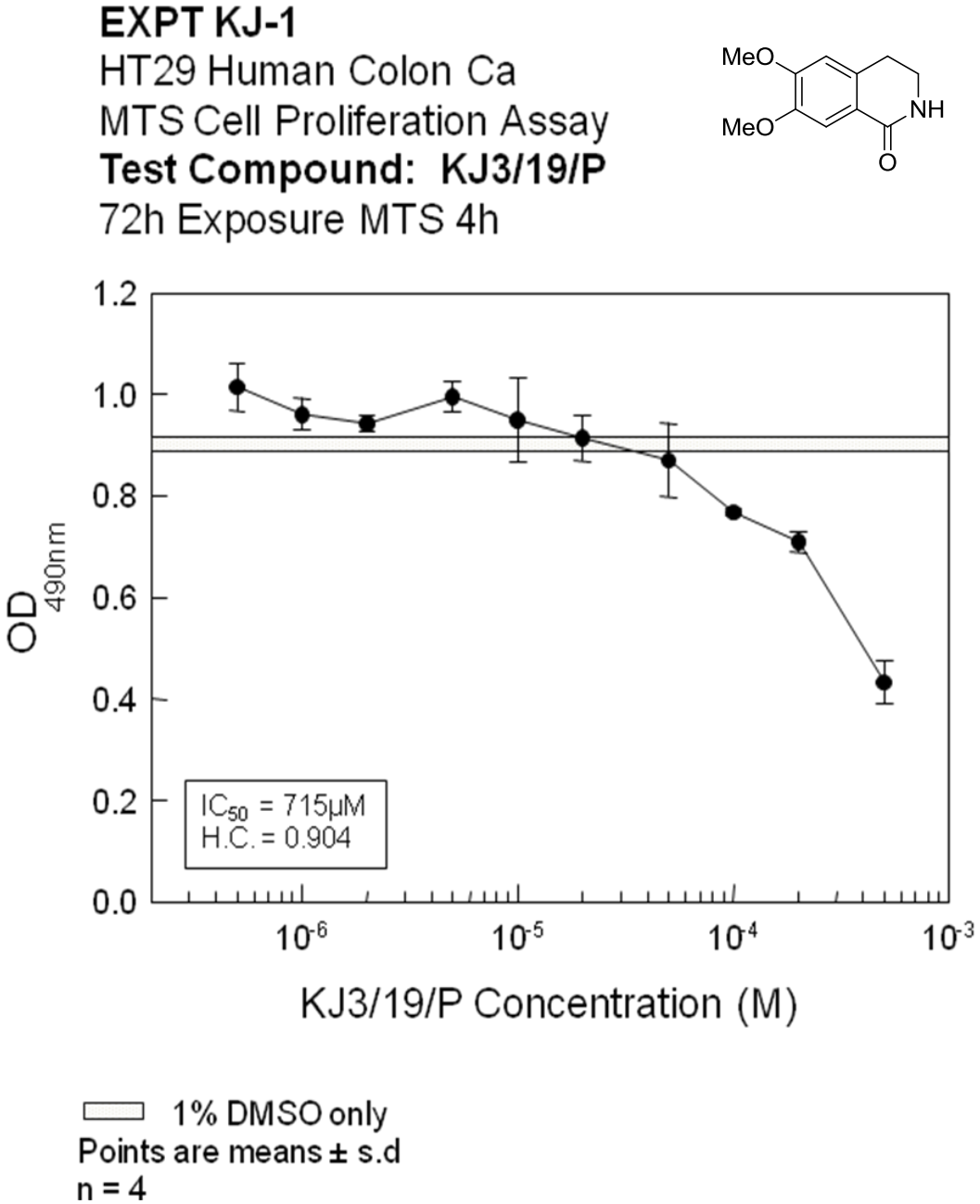
EXPT KJ-9
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ3/22/P
72h Exposure MTS 2h





1% DMSO only
Points are means ± s.d
n = 4

6,7-Dimethoxy-3,4-dihydroisoquinolin-1(2H)-one (147)



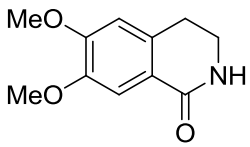
EXPT KJ-9

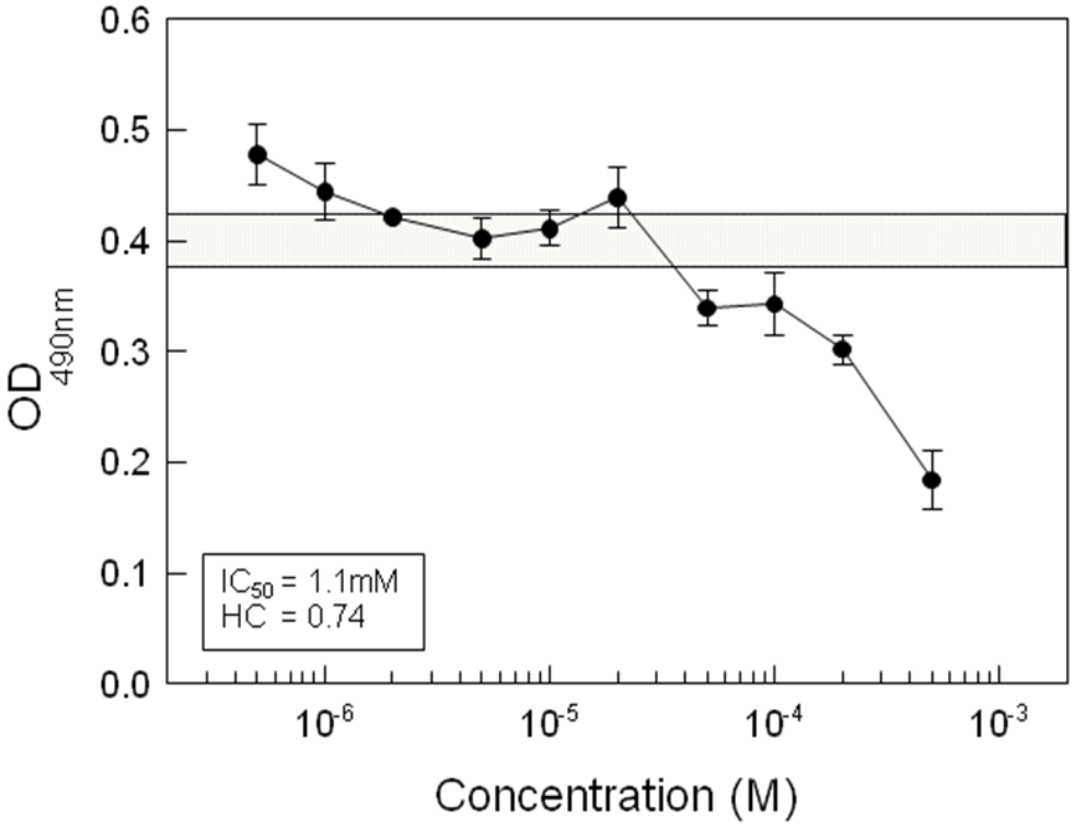
HT29 Human Colon Ca

MTS Cell Proliferation Assay

Test Compound: KJ3/19/P

72h Exposure MTS 2h



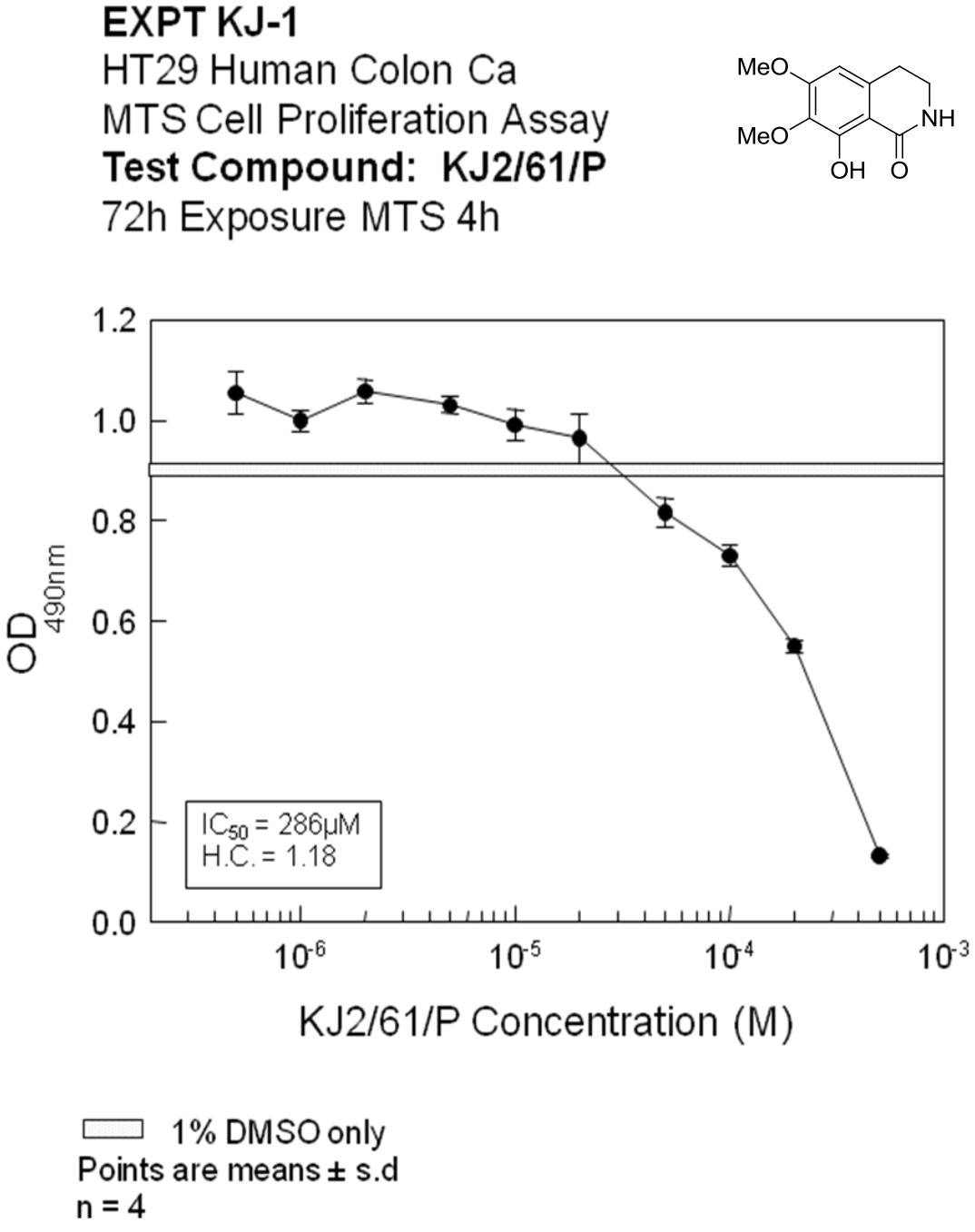


1% DMSO only

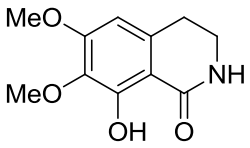
Points are means ± s.d

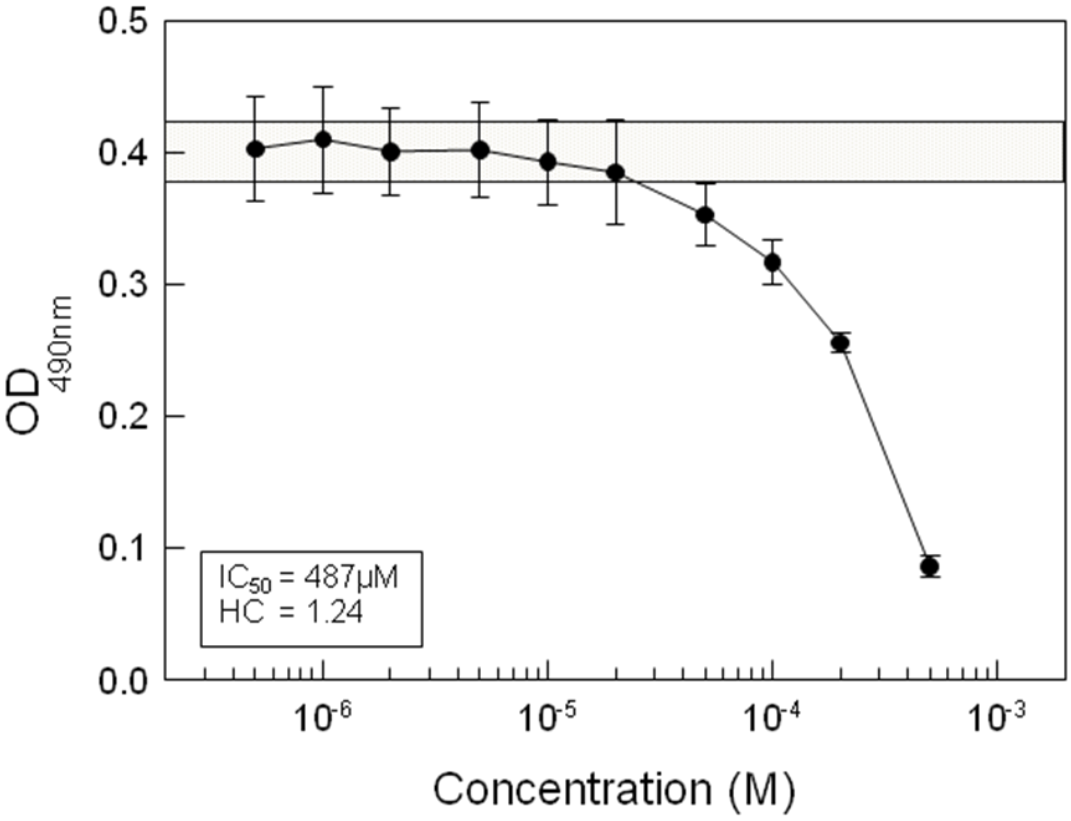
n = 4

6,7-Dimethoxy-8-hydroxy-3,4-dihydroisoquinolin-1(2H)-one (151)



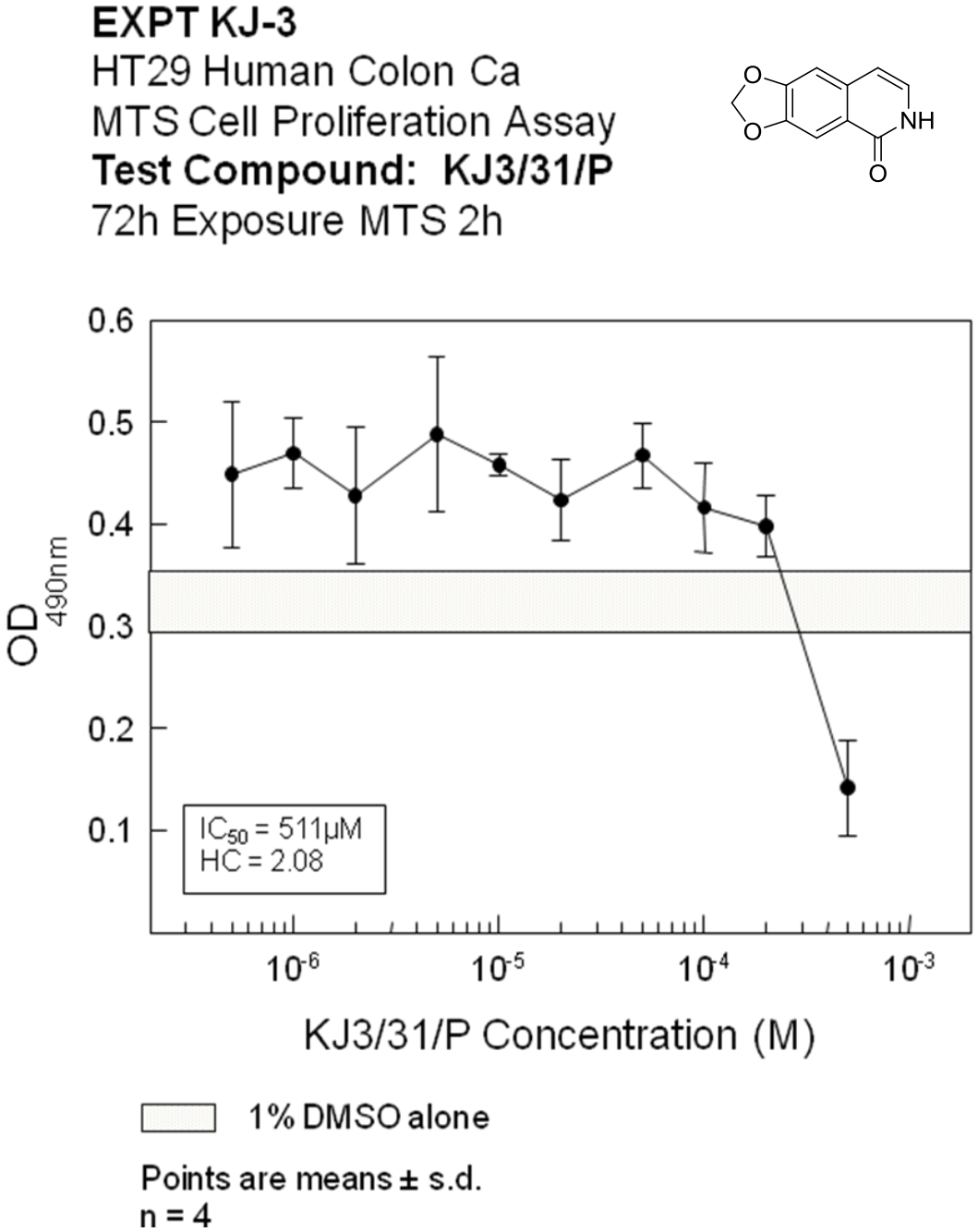
EXPT KJ-9
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ4/60/P
72h Exposure MTS 2h



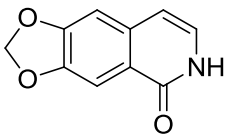


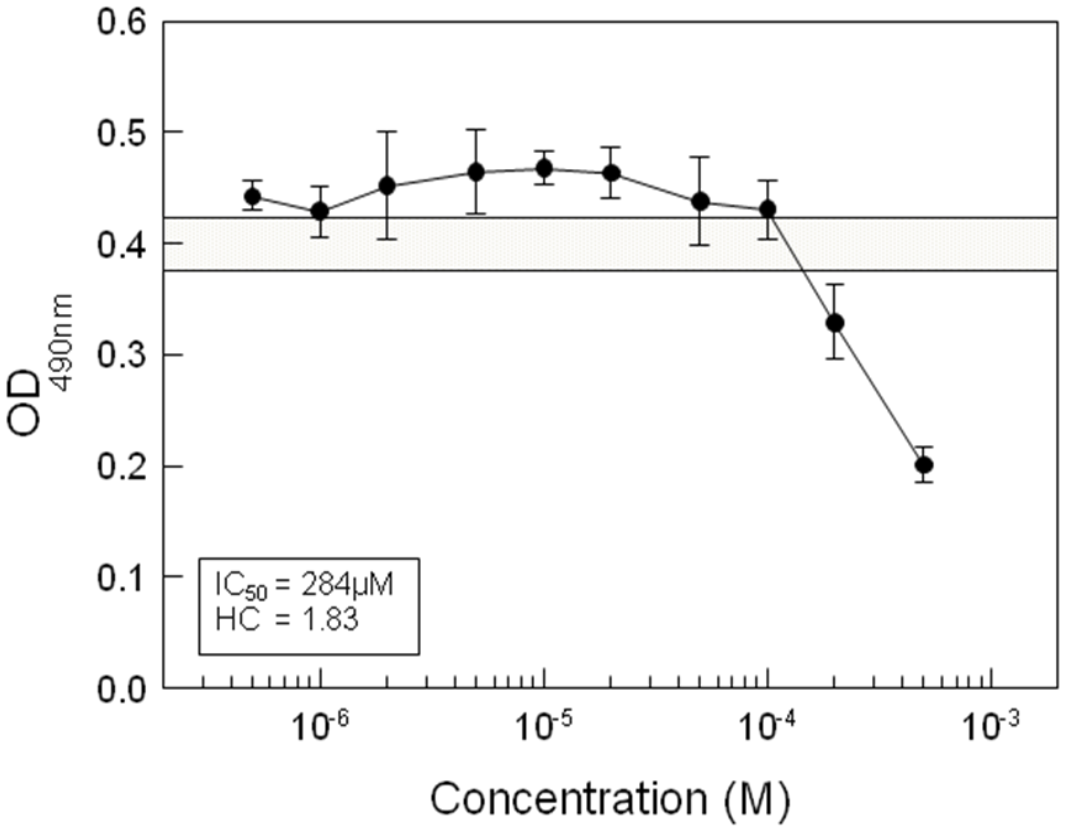
1% DMSO only
Points are means ± s.d
n = 4

6H-1,3-Dioxolo[4,5-g]isoquinolin-5-one (172)



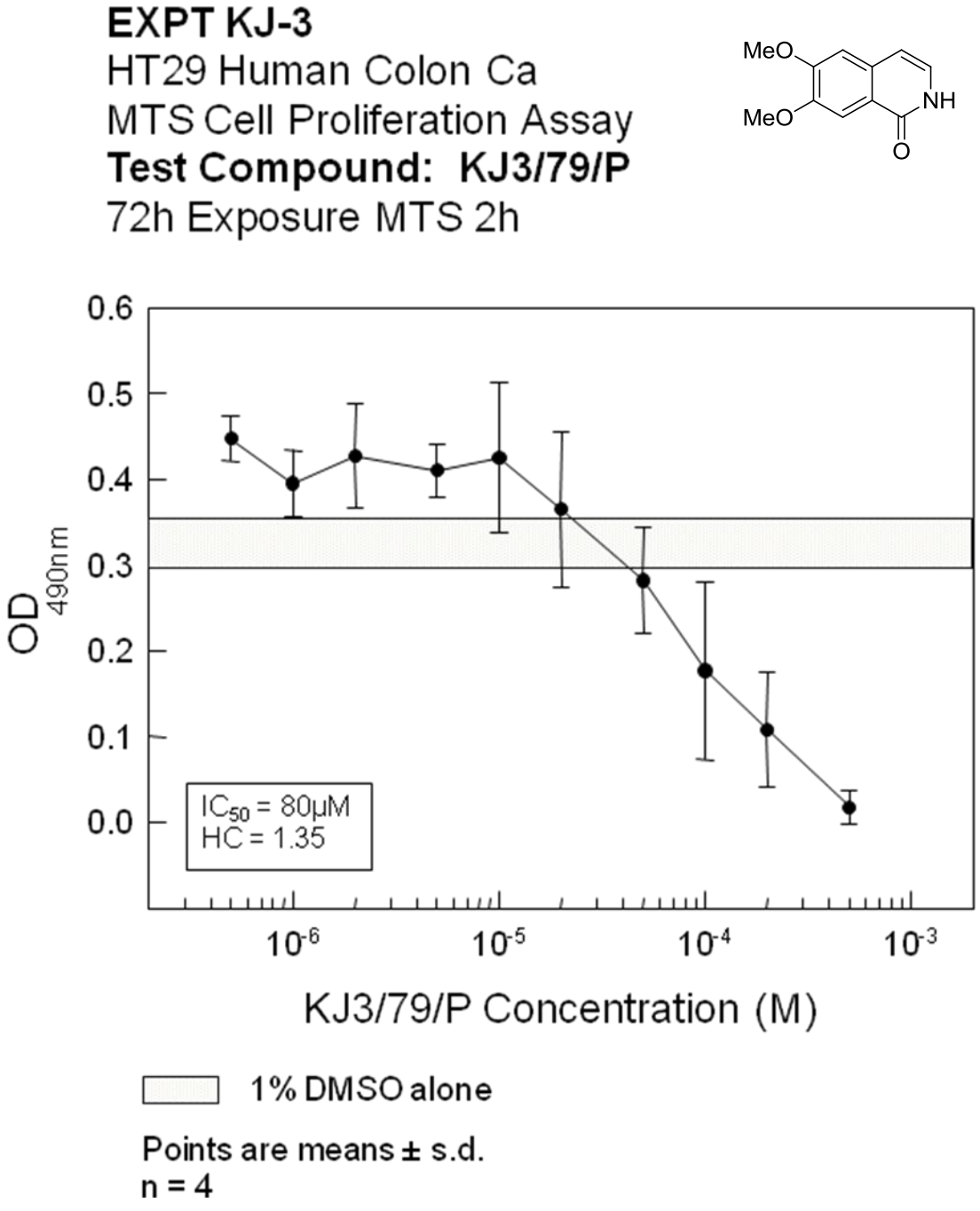
EXPT KJ-9
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ4/62/P
72h Exposure MTS 2h



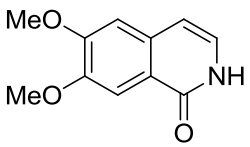


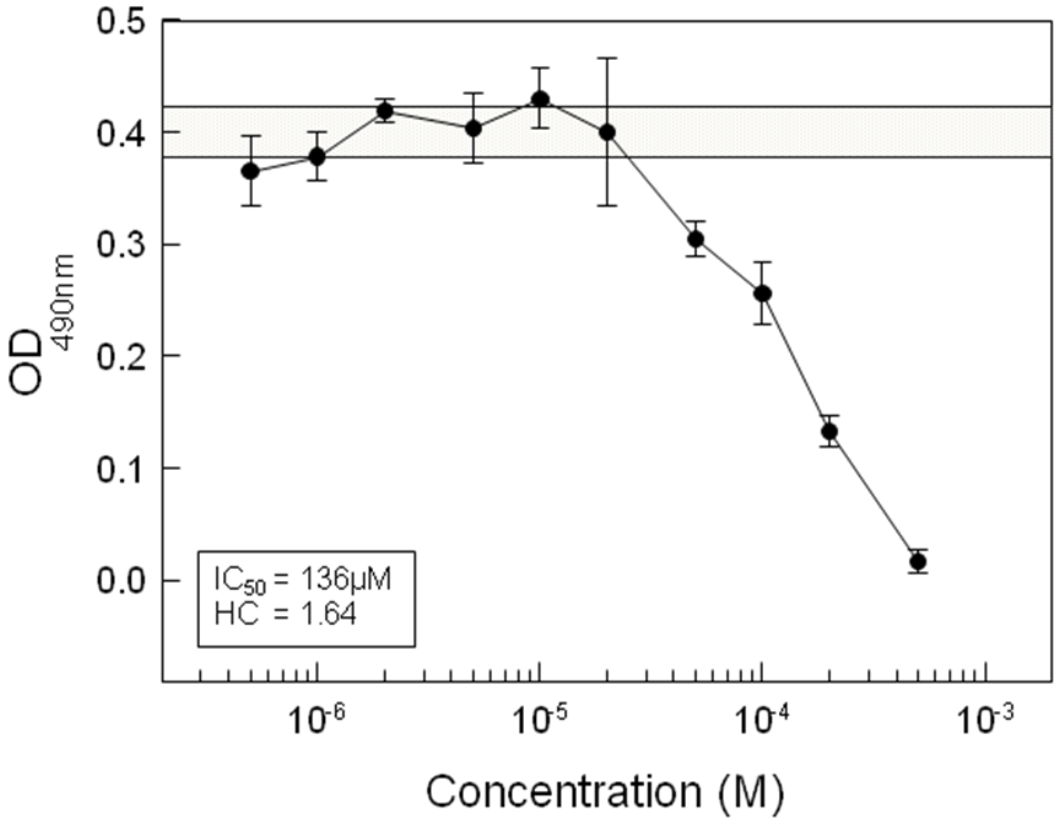
1% DMSO only
Points are means ± s.d
n = 4

6,7-Dimethoxyisoquinolin-1(2H)-one (173)



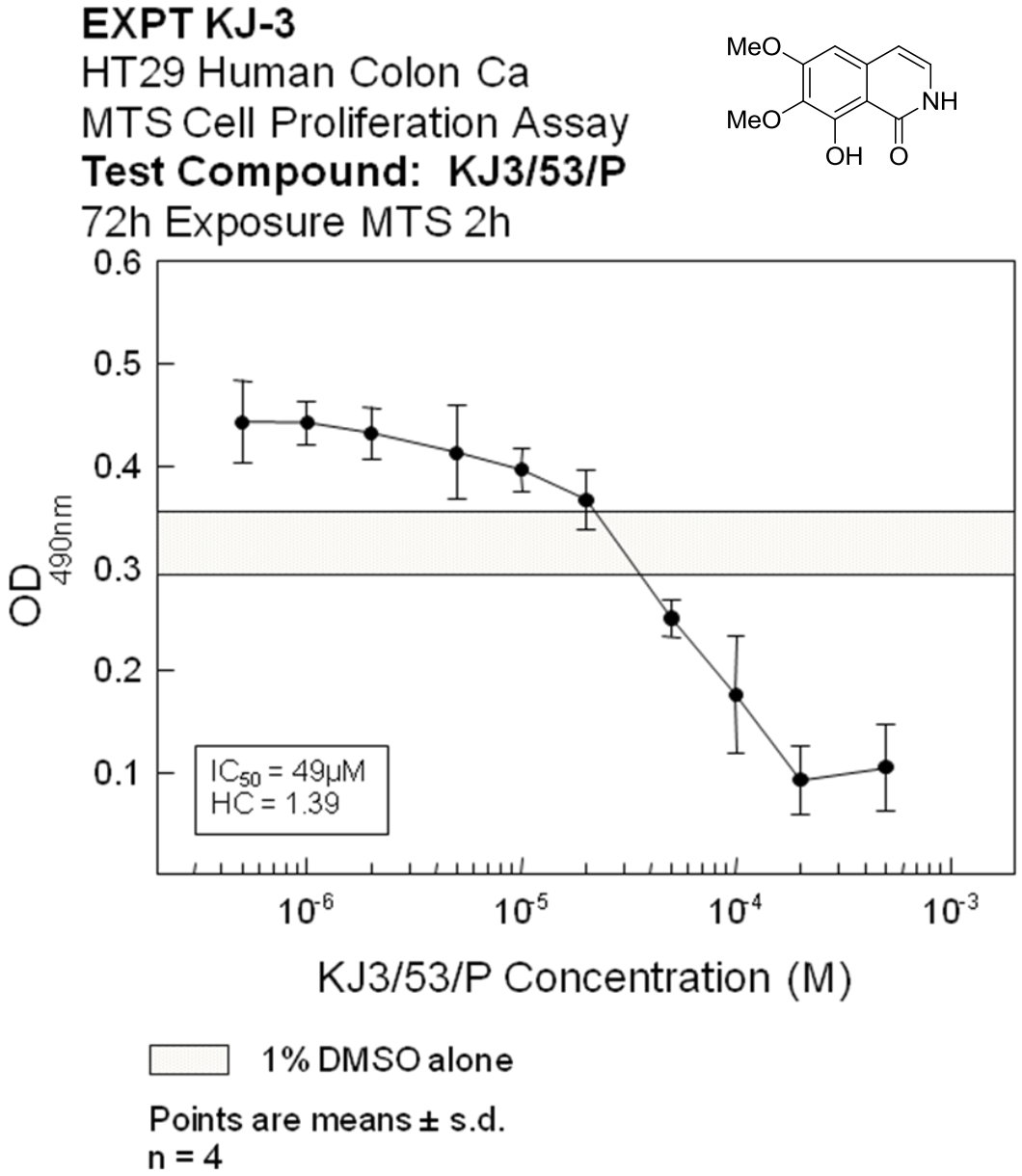
EXPT KJ-9
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ3/79/P
72h Exposure MTS 2h



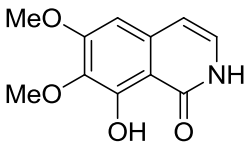


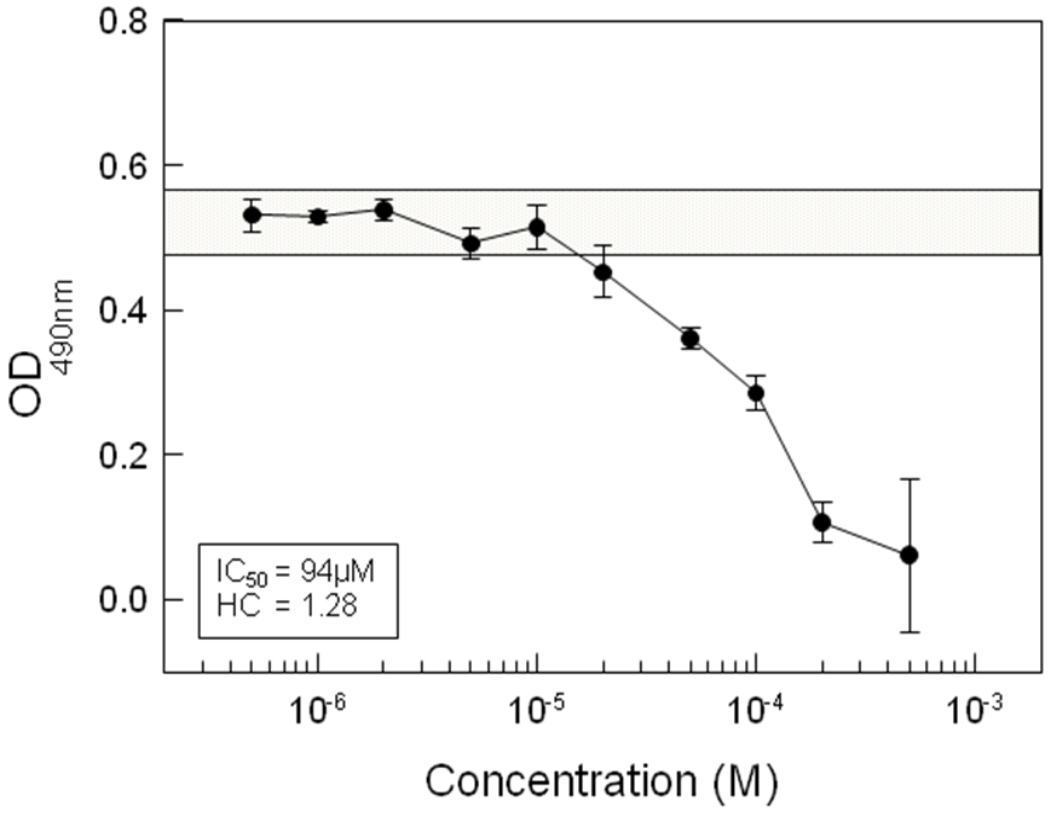
1% DMSO only
Points are means ± s.d
n = 4

6,7-Dimethoxy-8-hydroxyisoquinolin-1(2H)-one (174)



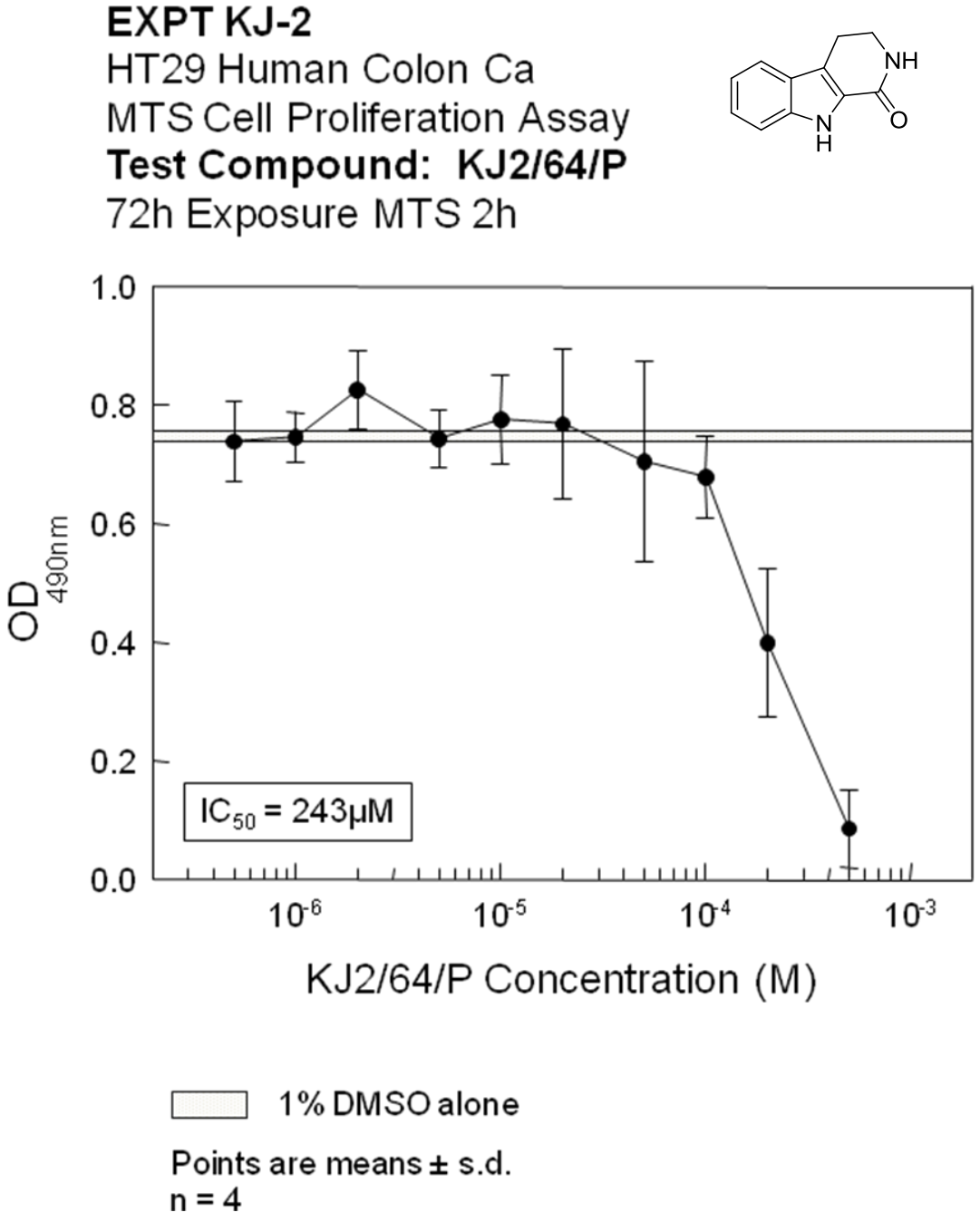
EXPT KJ-10
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ5/56/P
72h Exposure MTS 2h



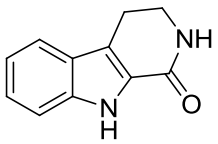


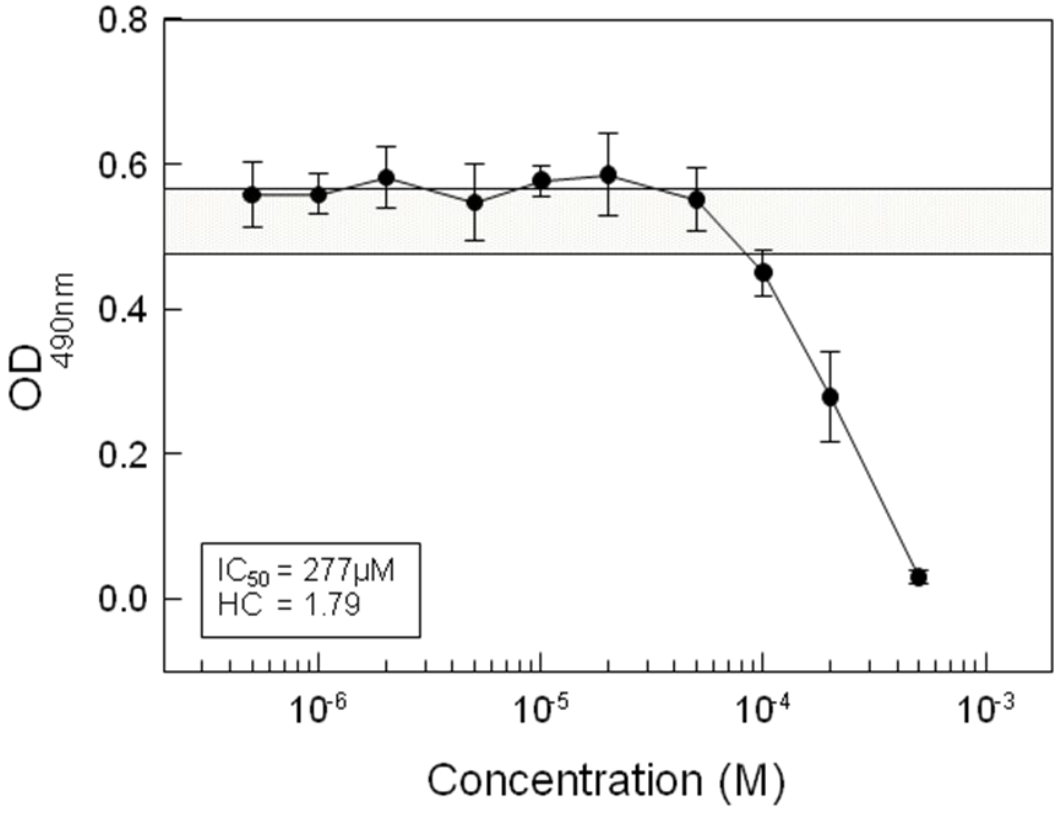
1% DMSO only
Points are means ± s.d
n = 4

2,3,4,9-Tetrahydro-β-carbolin-1-one (153)



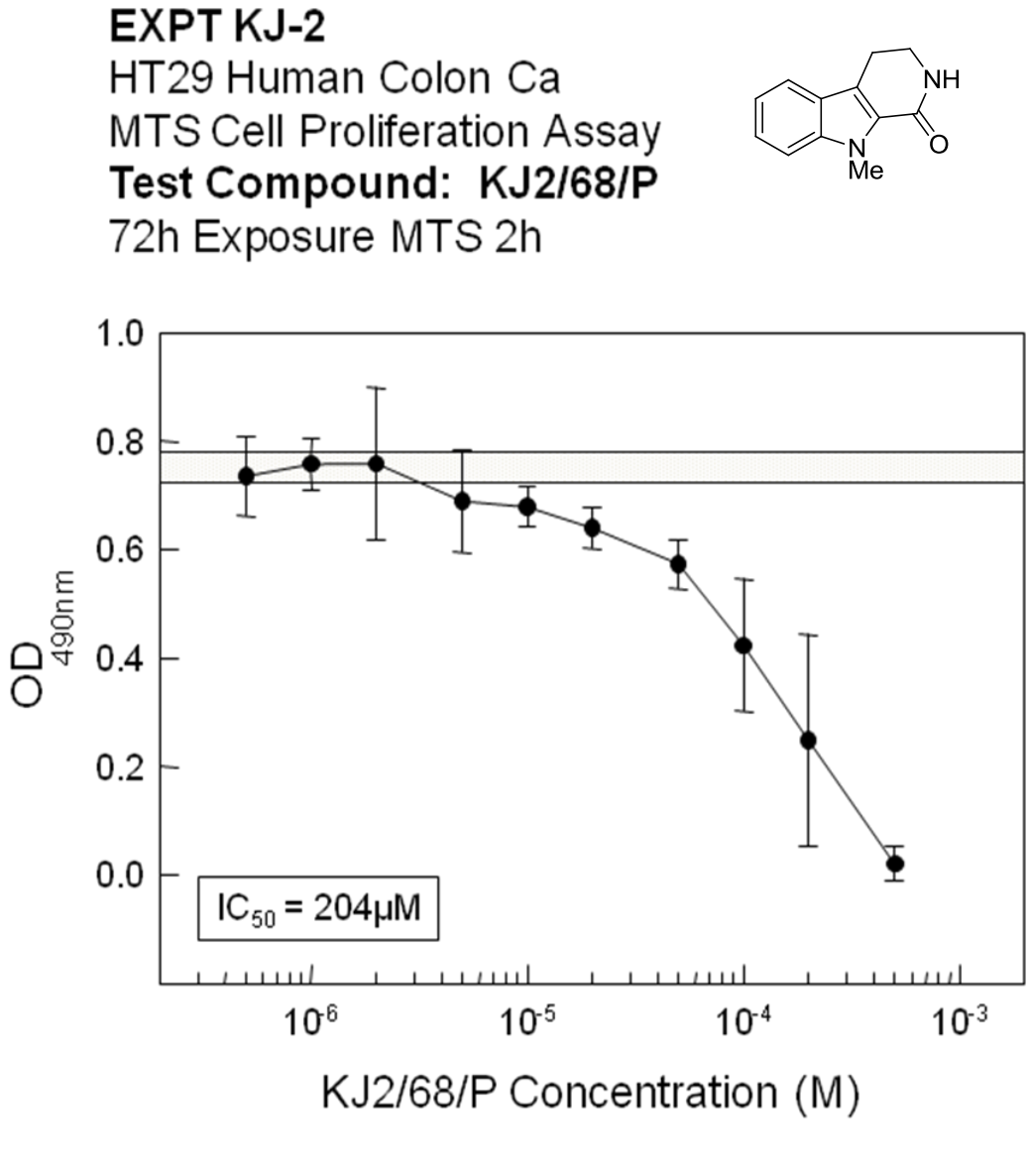
EXPT KJ-10
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ6/24/P
72h Exposure MTS 2h



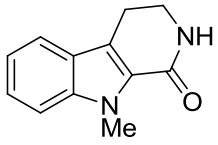


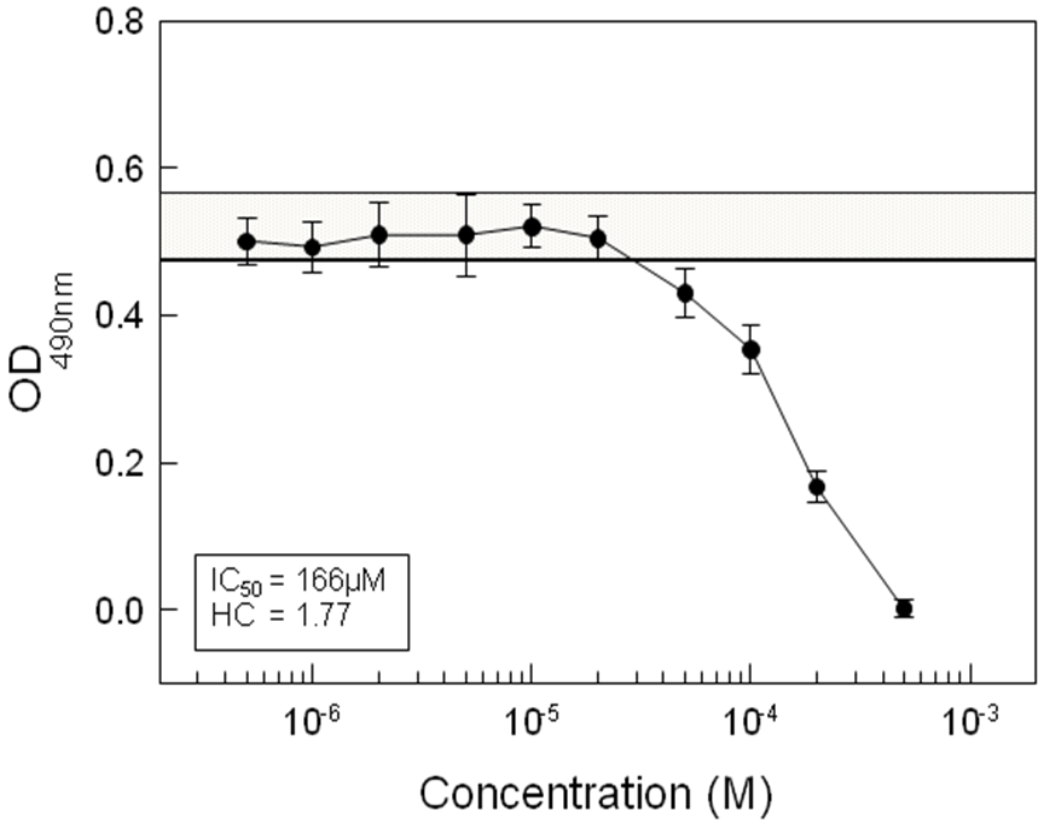
1% DMSO only
Points are means ± s.d
n = 4

9-Methyl-2,3,4,9-tetrahydro-β-carbolin-1-one (160)



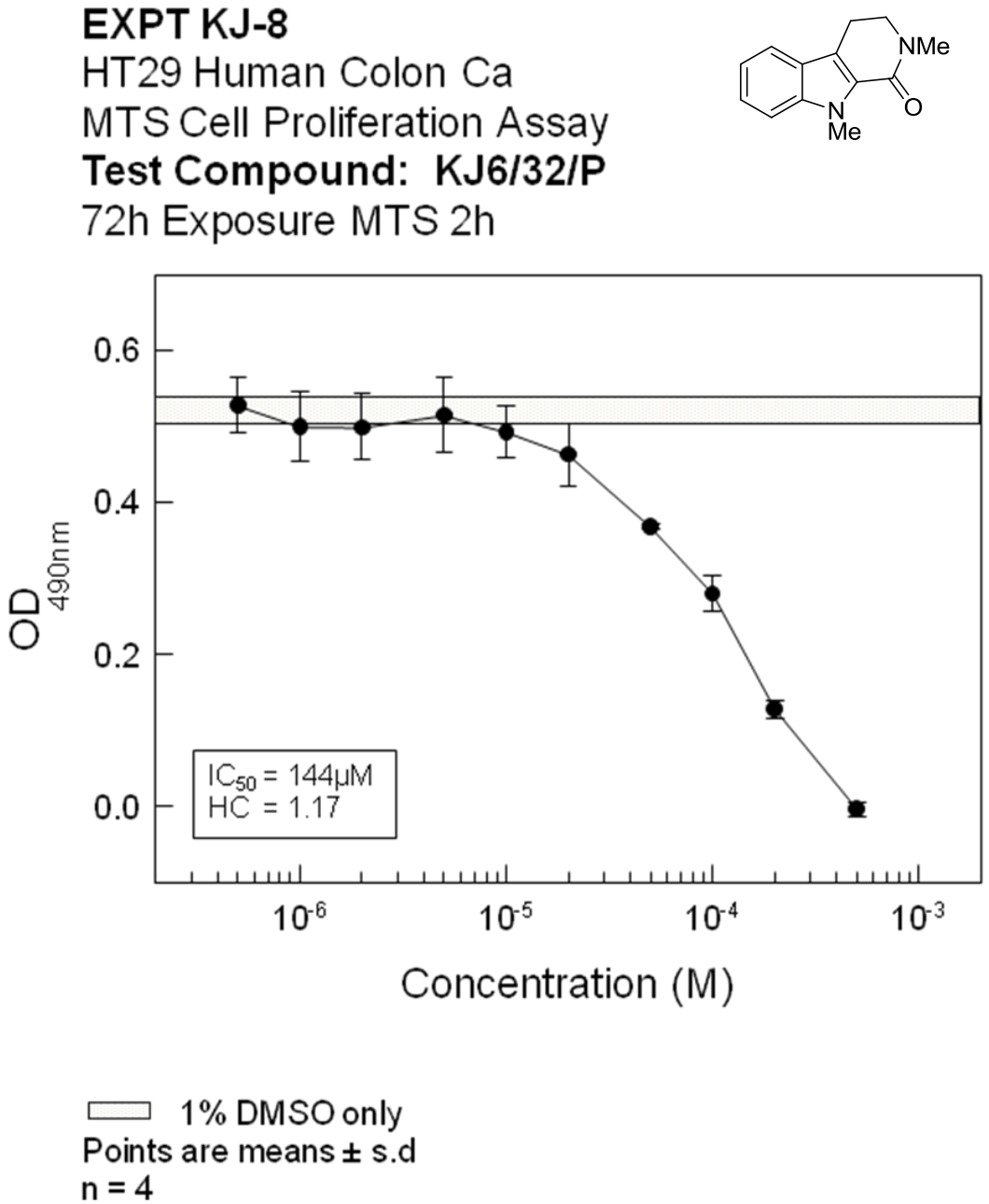
EXPT KJ-10
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ6/30/P
72h Exposure MTS 2h



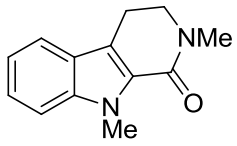


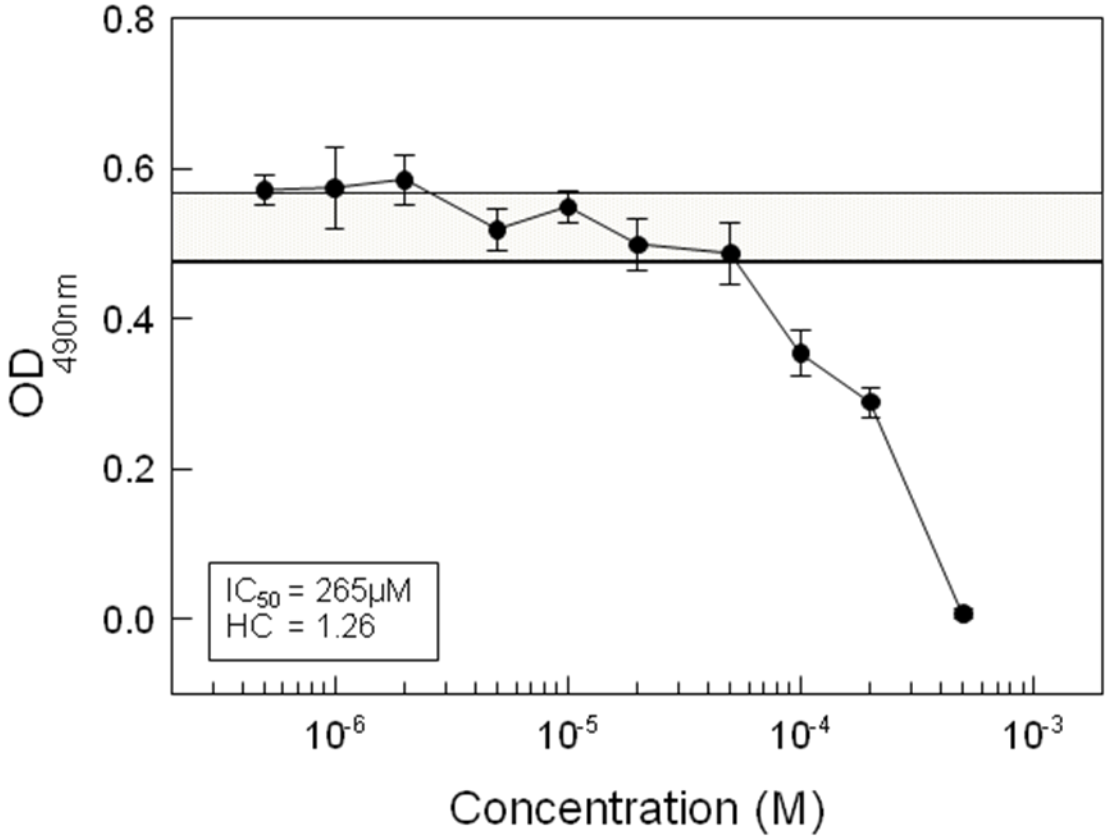
1% DMSO only
Points are means ± s.d
n = 4

2,9-Dimethyl-2,3,4,9-tetrahydro-β-carbolin-1-one (161)



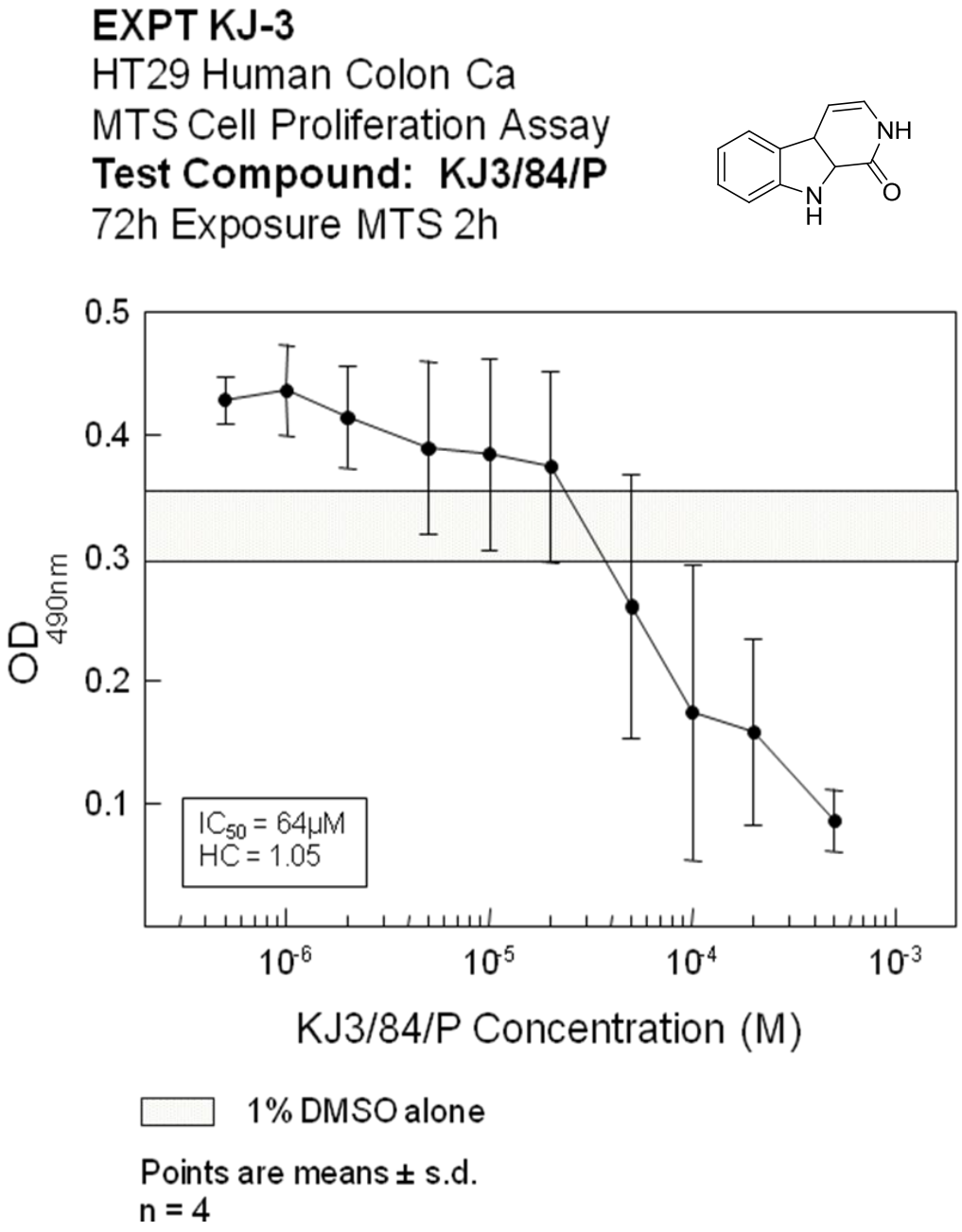
EXPT KJ-10
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ6/32/P
72h Exposure MTS 2h



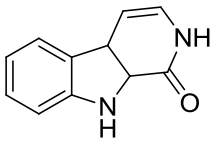


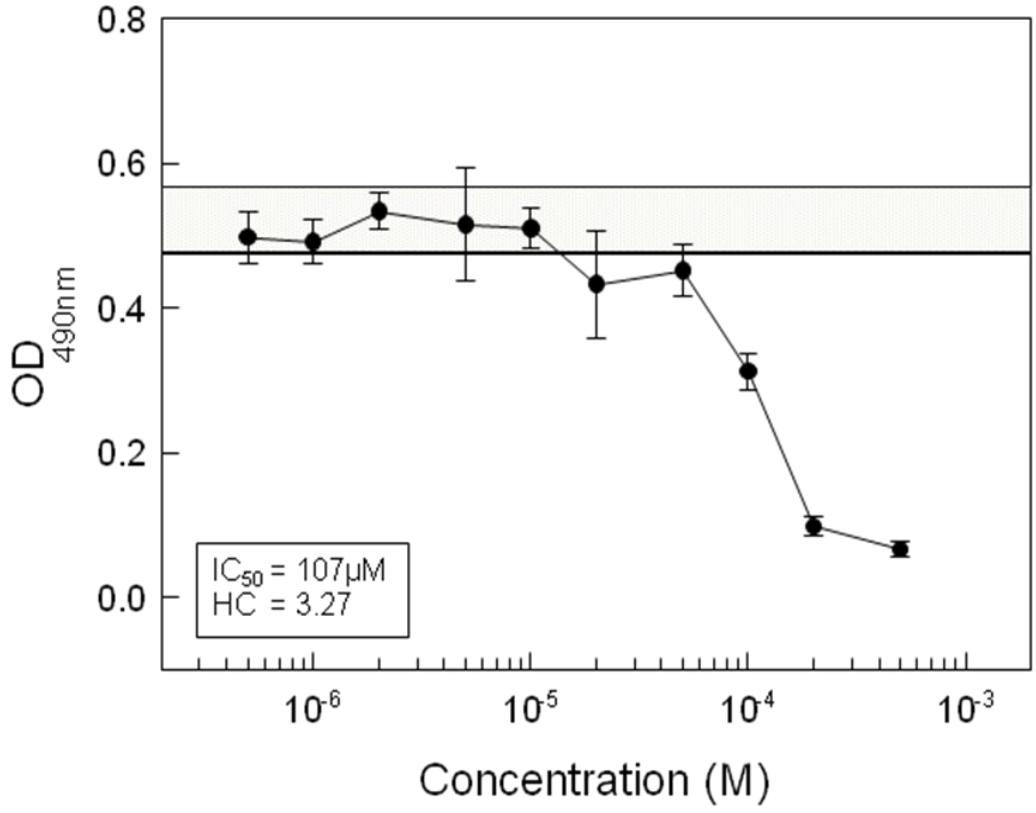
1% DMSO only
Points are means ± s.d
n = 4

2,9-Dihydro-1H-pyrido[3,4-b]indol-1-one (175)



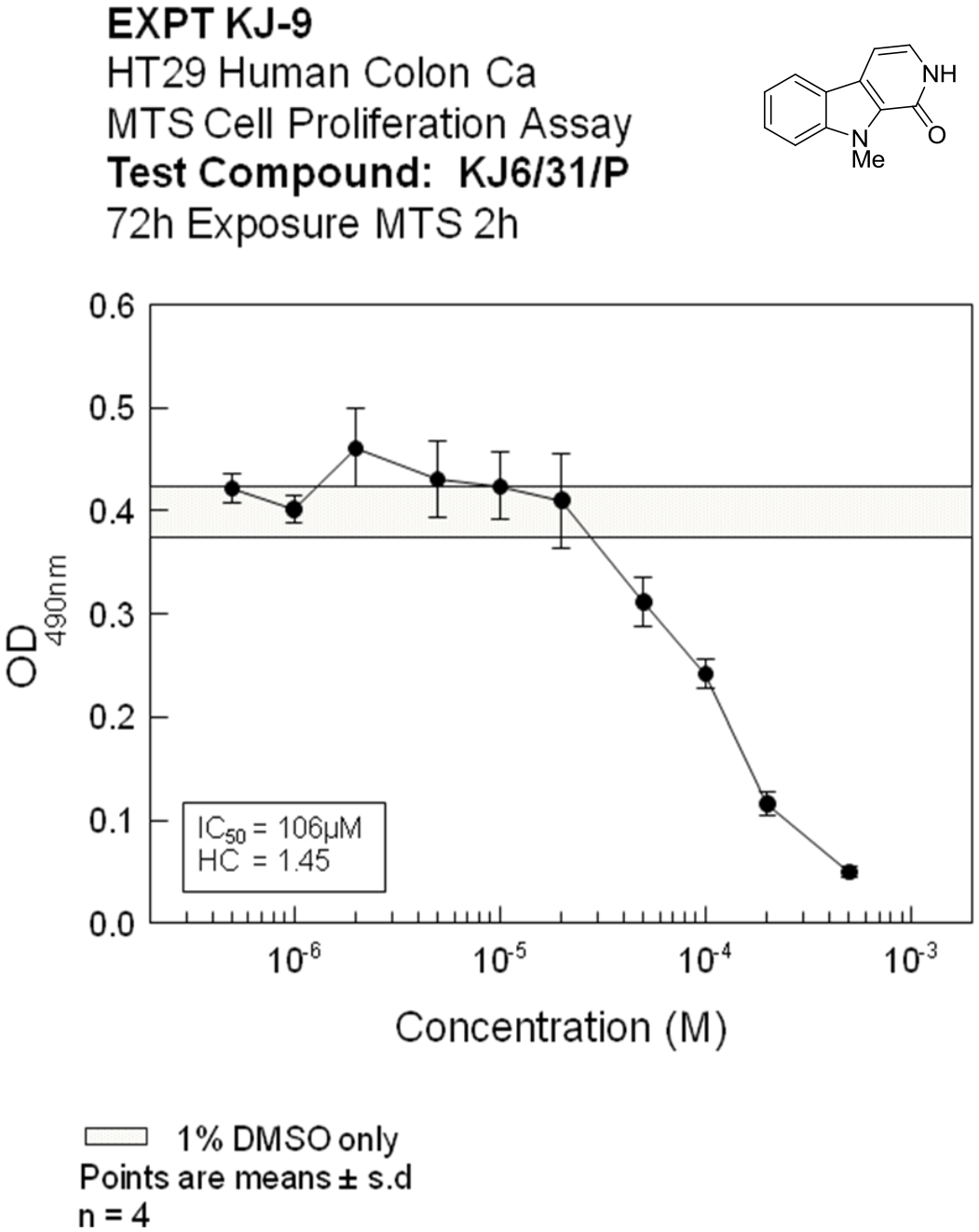
EXPT KJ-10
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ6/29/P
72h Exposure MTS 2h



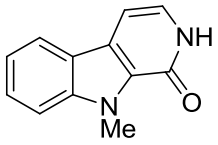


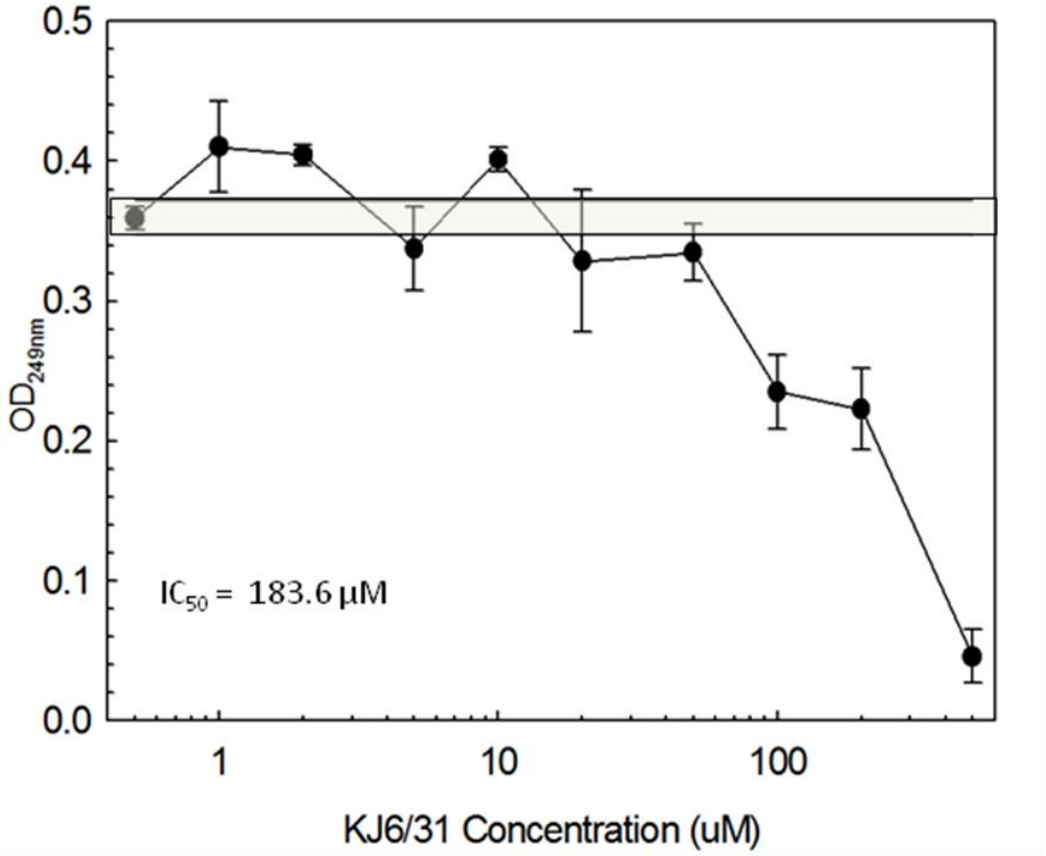
1% DMSO only
Points are means ± s.d
n = 4

9-Methyl-2,9-Dihydro-1H-pyrido[3,4-b]indol-1-one (176)



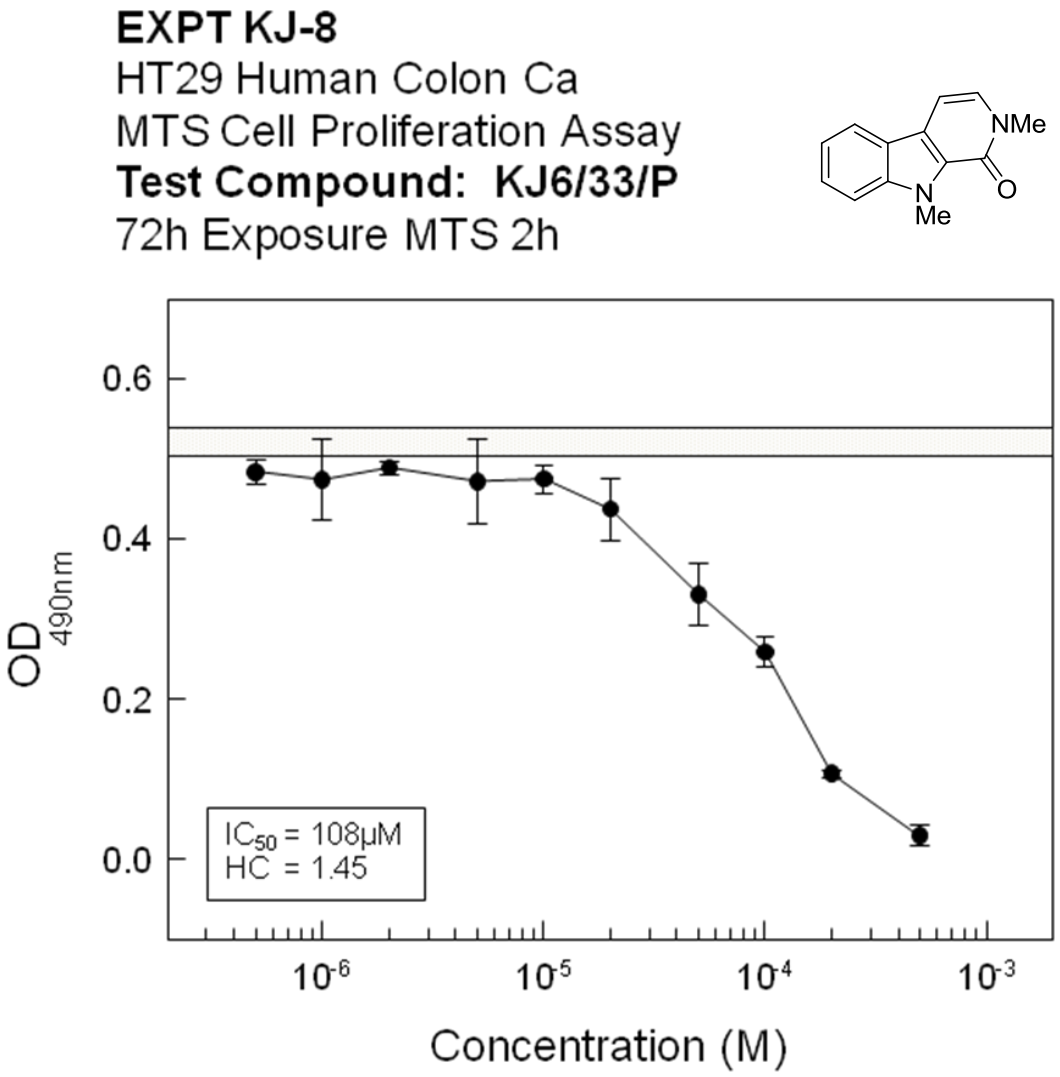
EXPT KJ-13
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ6/31/P
72h Exposure MTS 2h



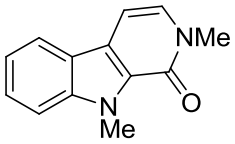


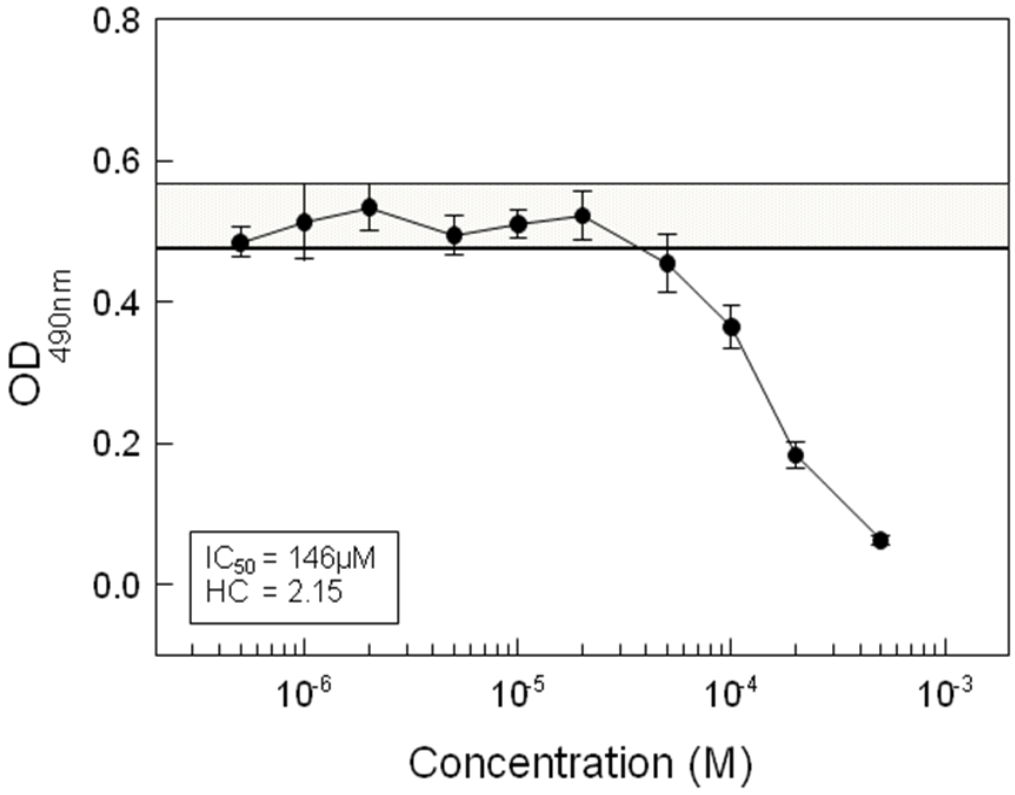
1% DMSO only
Points are means ± s.d
n = 4

2,9-Dimethyl-2,9-Dihydro-1H-pyrido[3,4-b]indol-1-one (177)



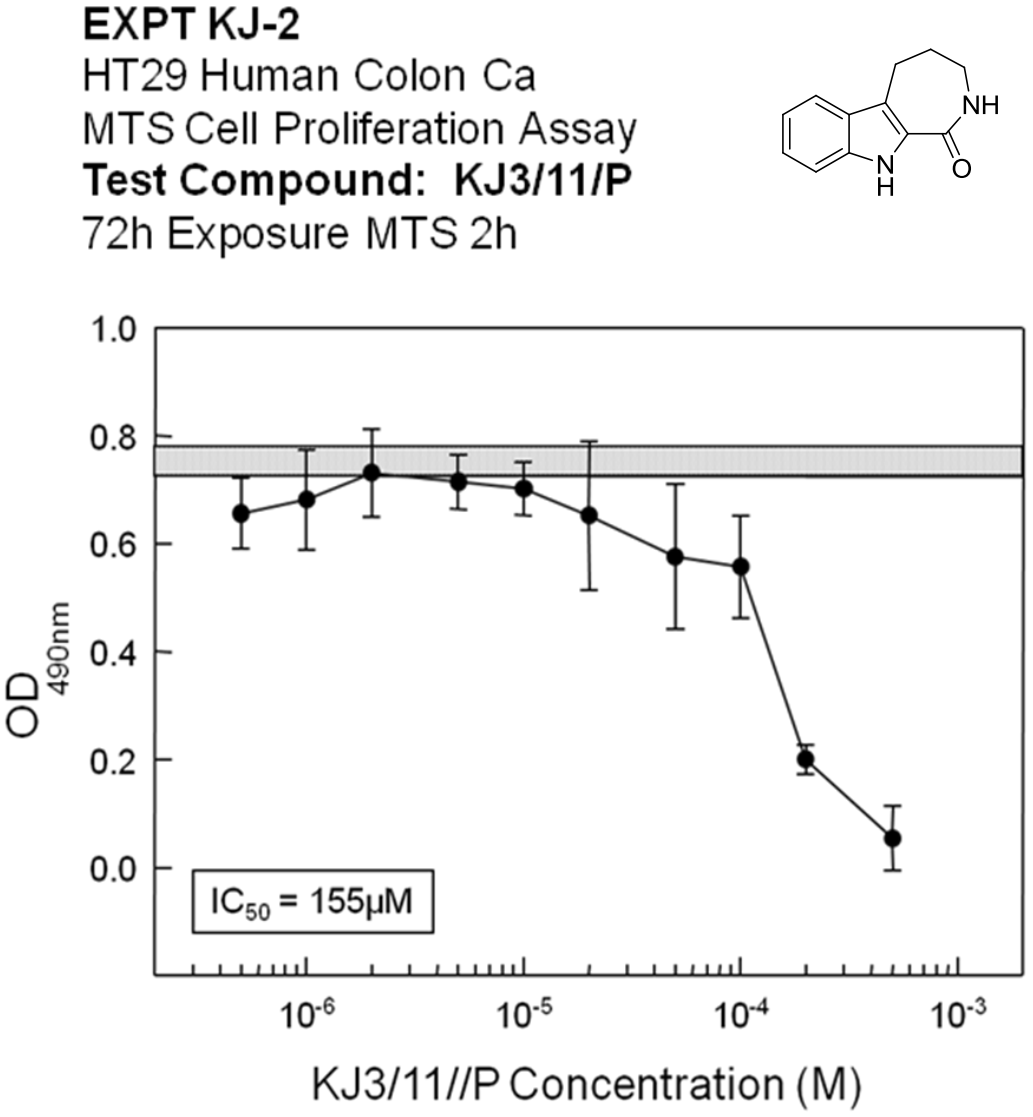
EXPT KJ-10
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ6/33/P
72h Exposure MTS 2h



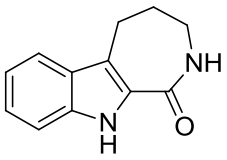


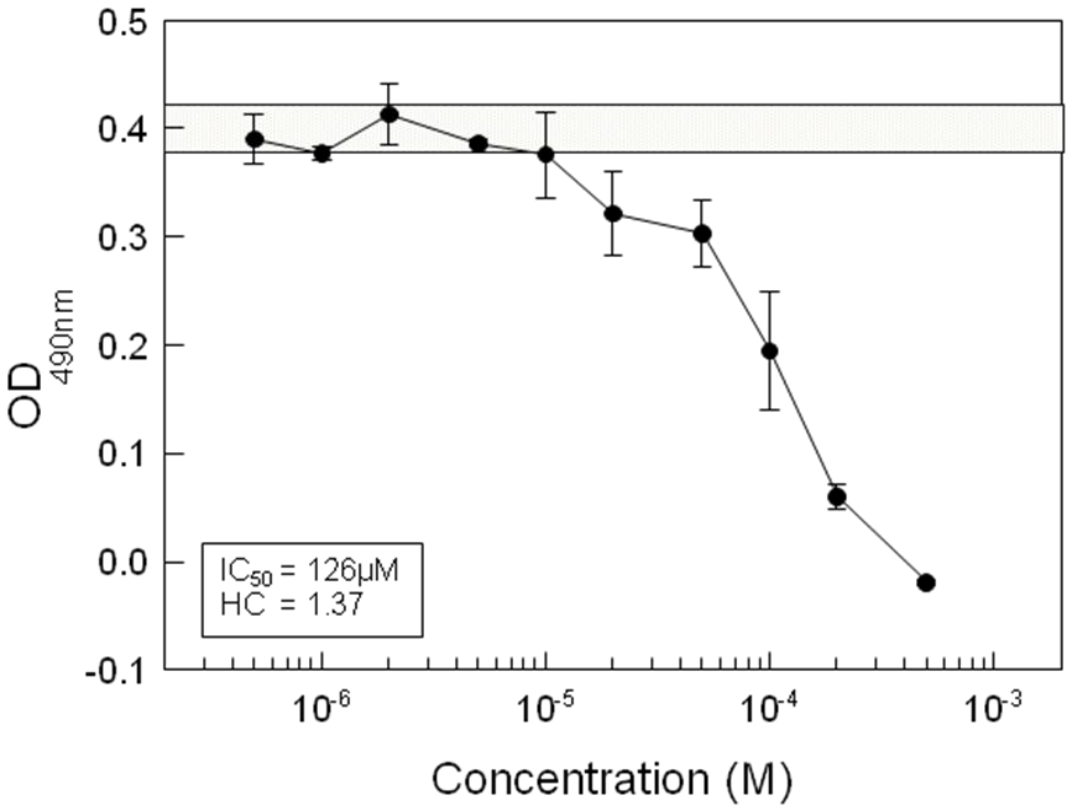
1% DMSO only
Points are means ± s.d
n = 4

3,4,5,10-Tetrahydro-2H-azepino[3,4-b]indol-1-one (163)



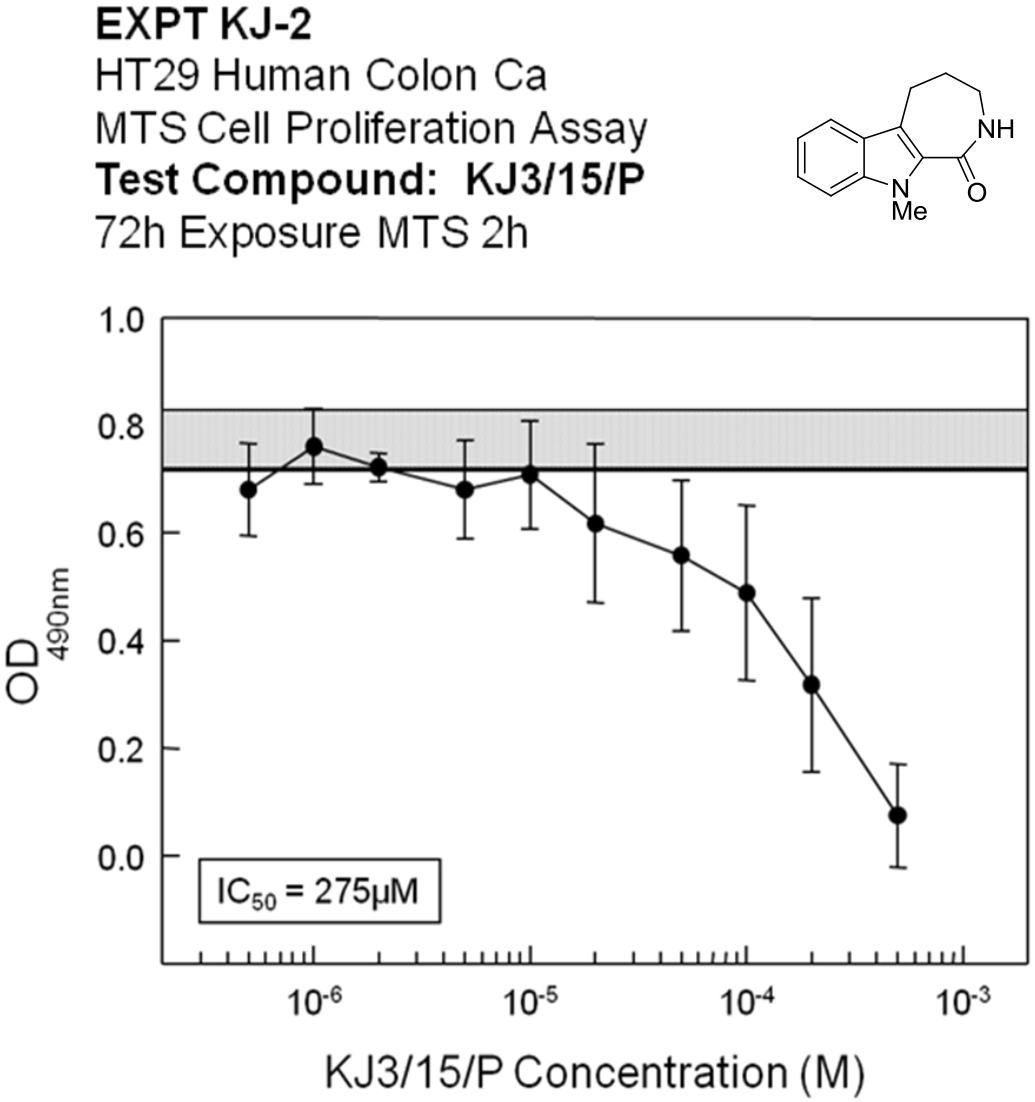
EXPT KJ-9
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ3/11/P
72h Exposure MTS 2h



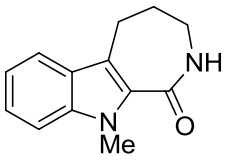


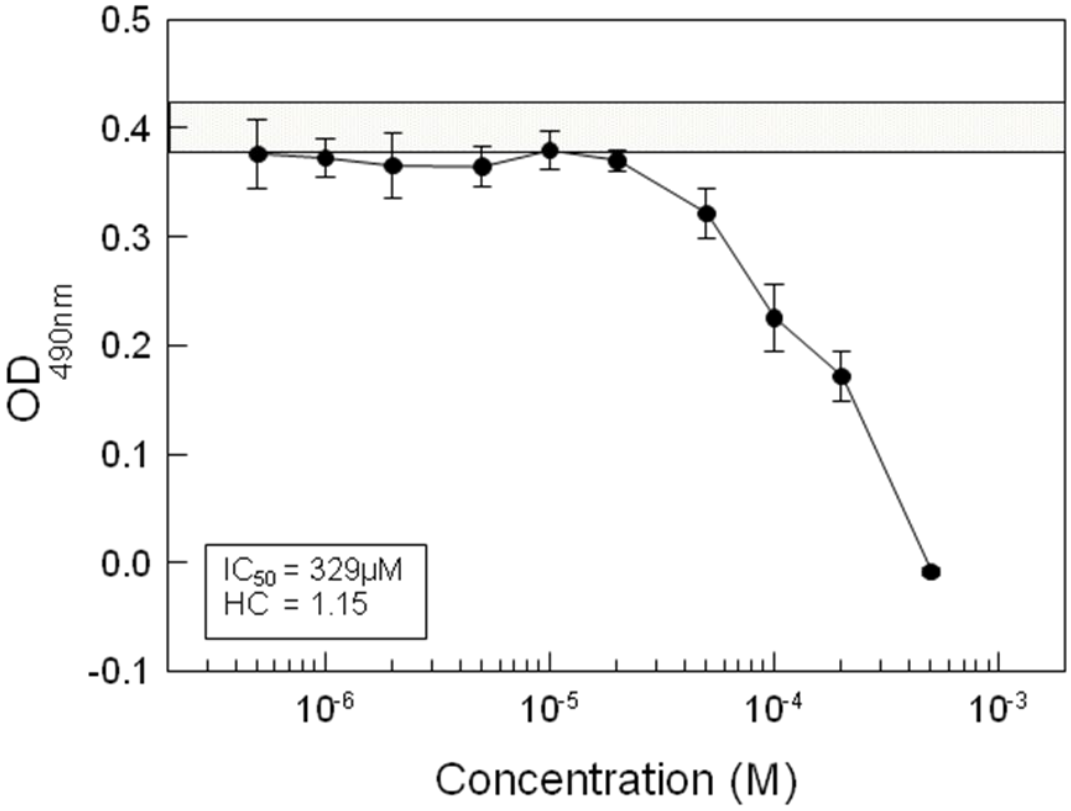
1% DMSO only
Points are means ± s.d
n = 4

10-Methyl-3,4,5,10-tetrahydro-2H-azepino[3,4-b]indol-1-one (166)



EXPT KJ-9
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ3/15/P
72h Exposure MTS 2h

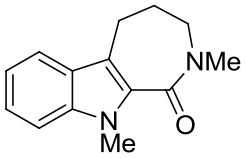


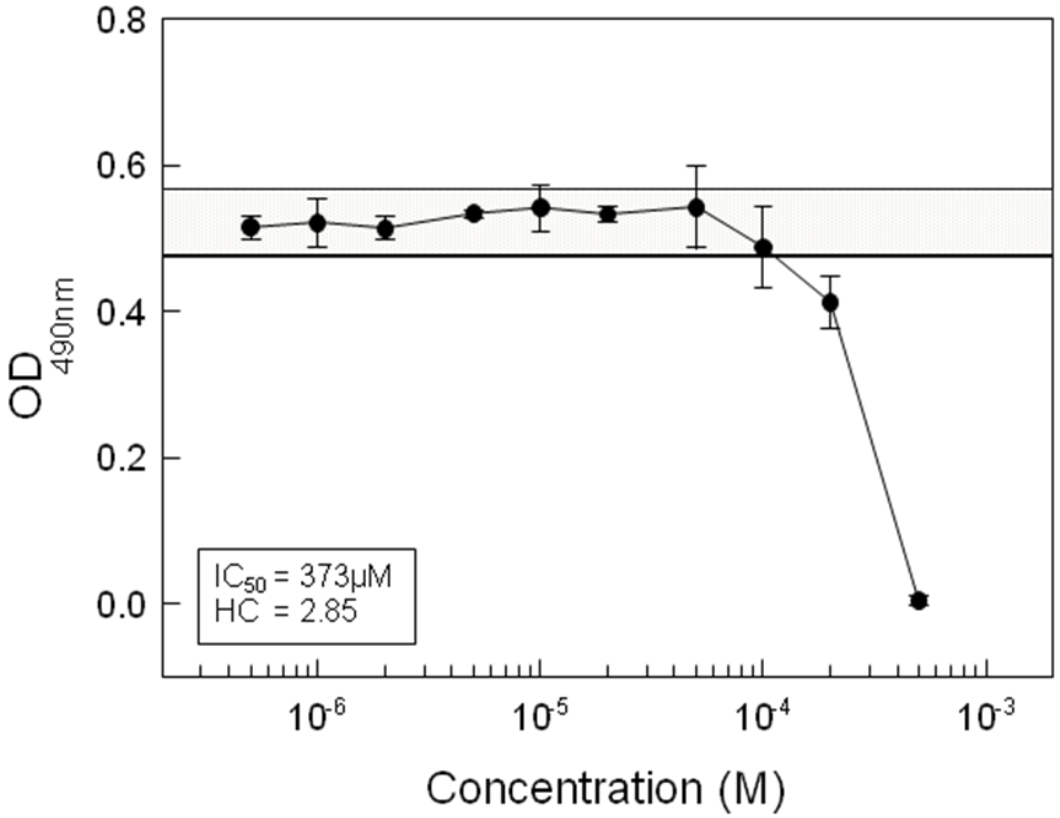


1% DMSO only
Points are means ± s.d
n = 4

2,10-Dimethyl-3,4,5,10-tetrahydro-2H-azepino[3,4-b]indol-1-one (167)

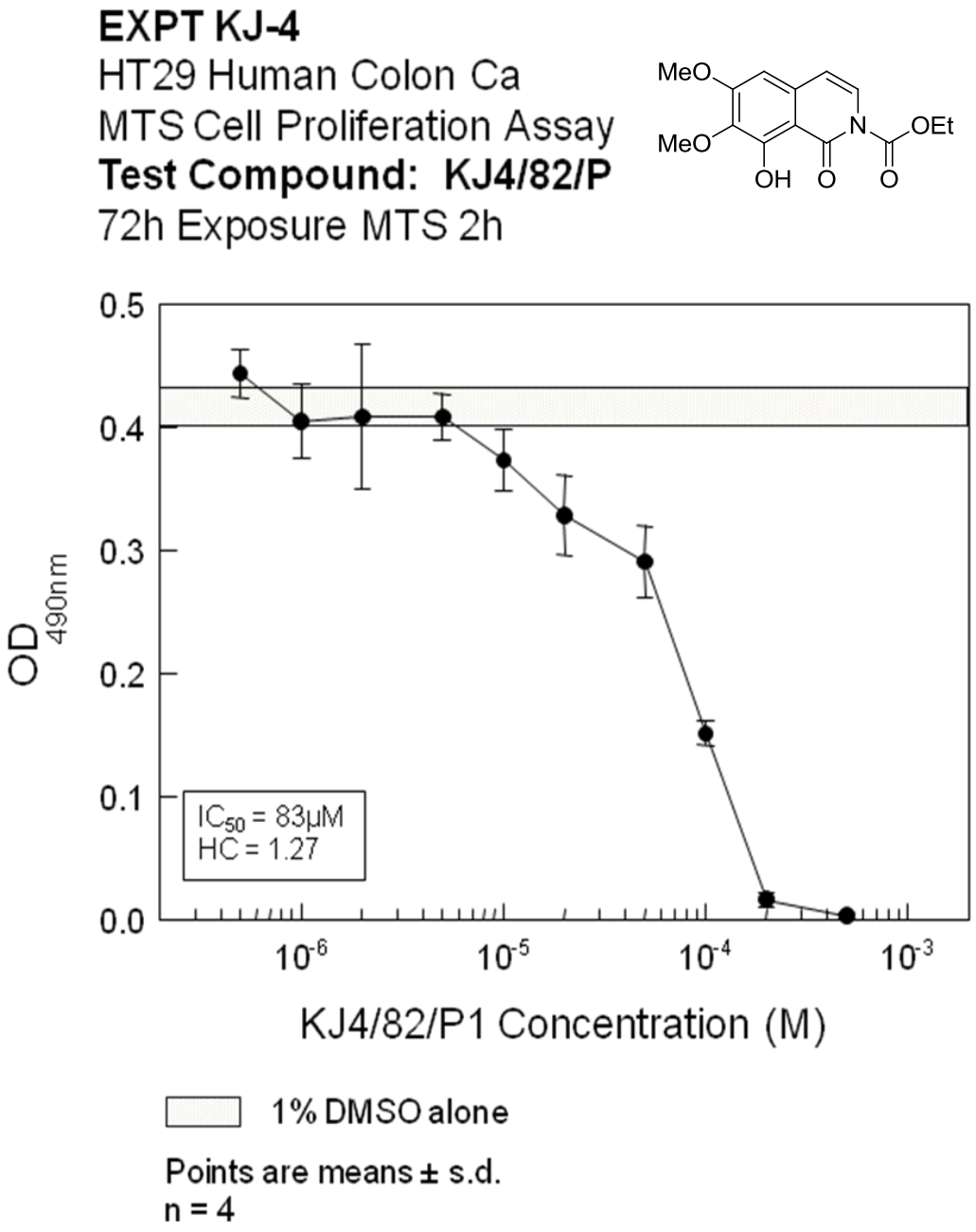
EXPT KJ-10
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ7/60/P
72h Exposure MTS 2h



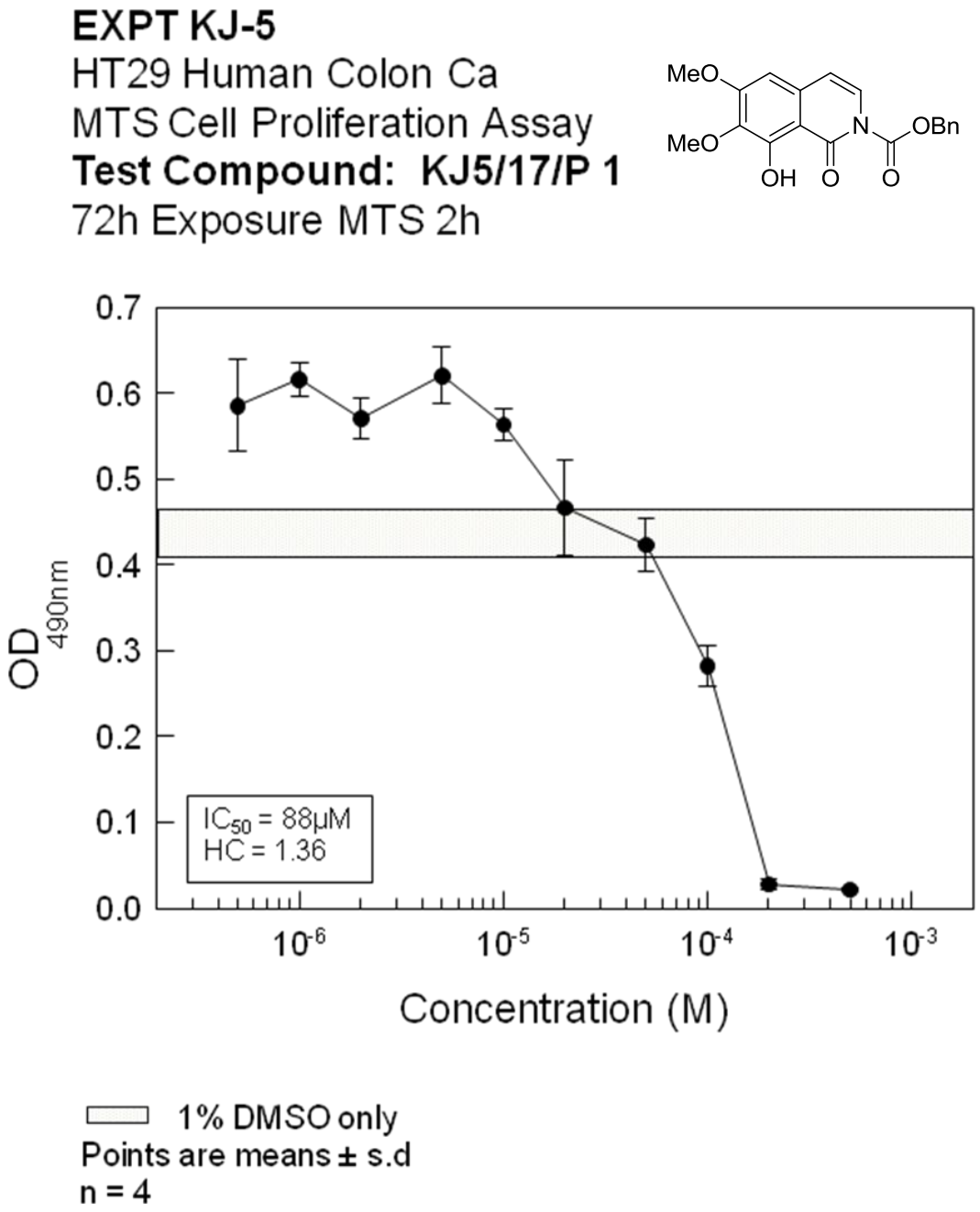


1% DMSO only
Points are means ± s.d
n = 4

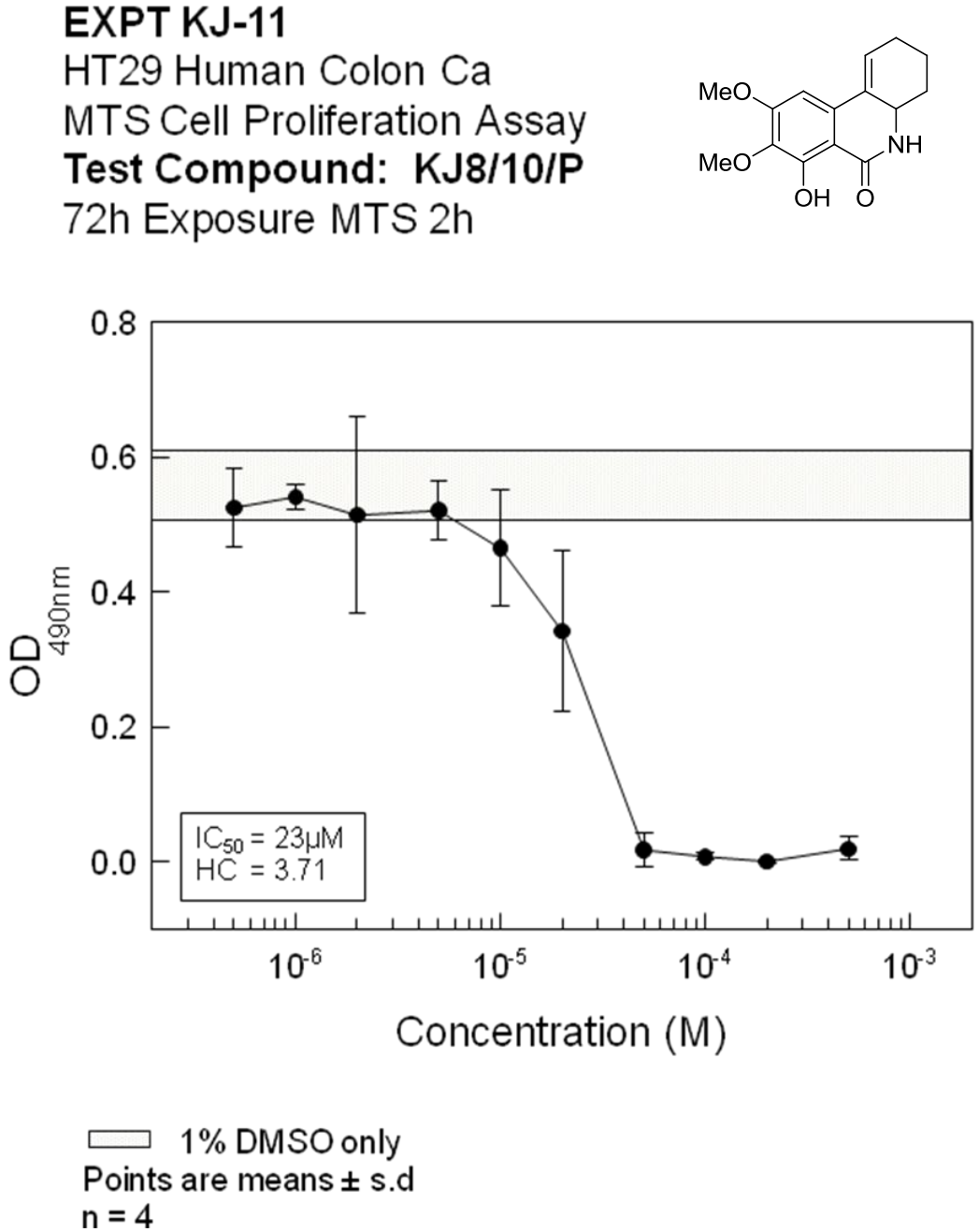
8-Hydroxy-6,7-dimethoxy-1-oxo-1*H*-isoquinoline-2-carboxylic acid ethyl ester (178)



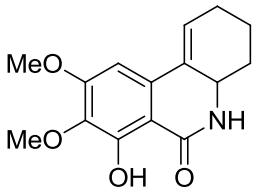
Benzyl 8-hydroxy-6,7-dimethoxy-1-oxoisoquinoline-2(1H)-carboxylate (179)

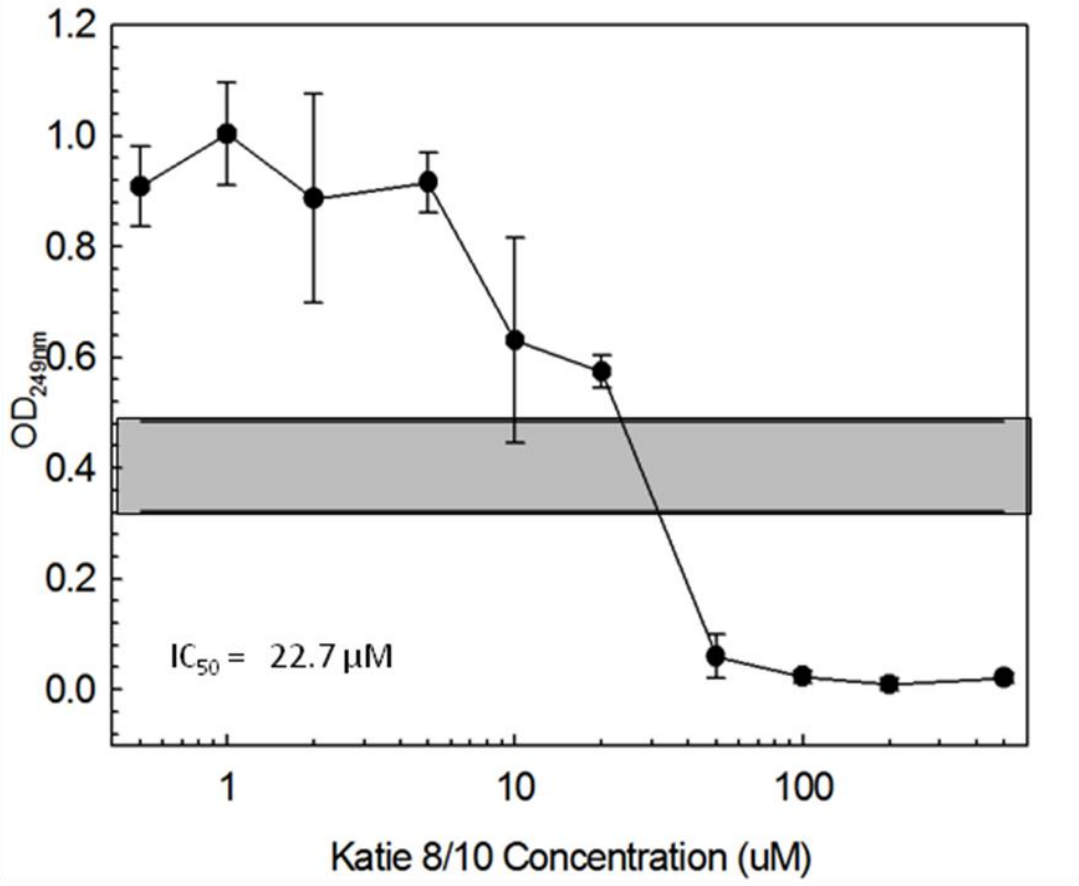


7-Hydroxy-8,9-dimethoxy-3,4,4a,5-tetrahydrophenanthridin-6(2H)-one (236)



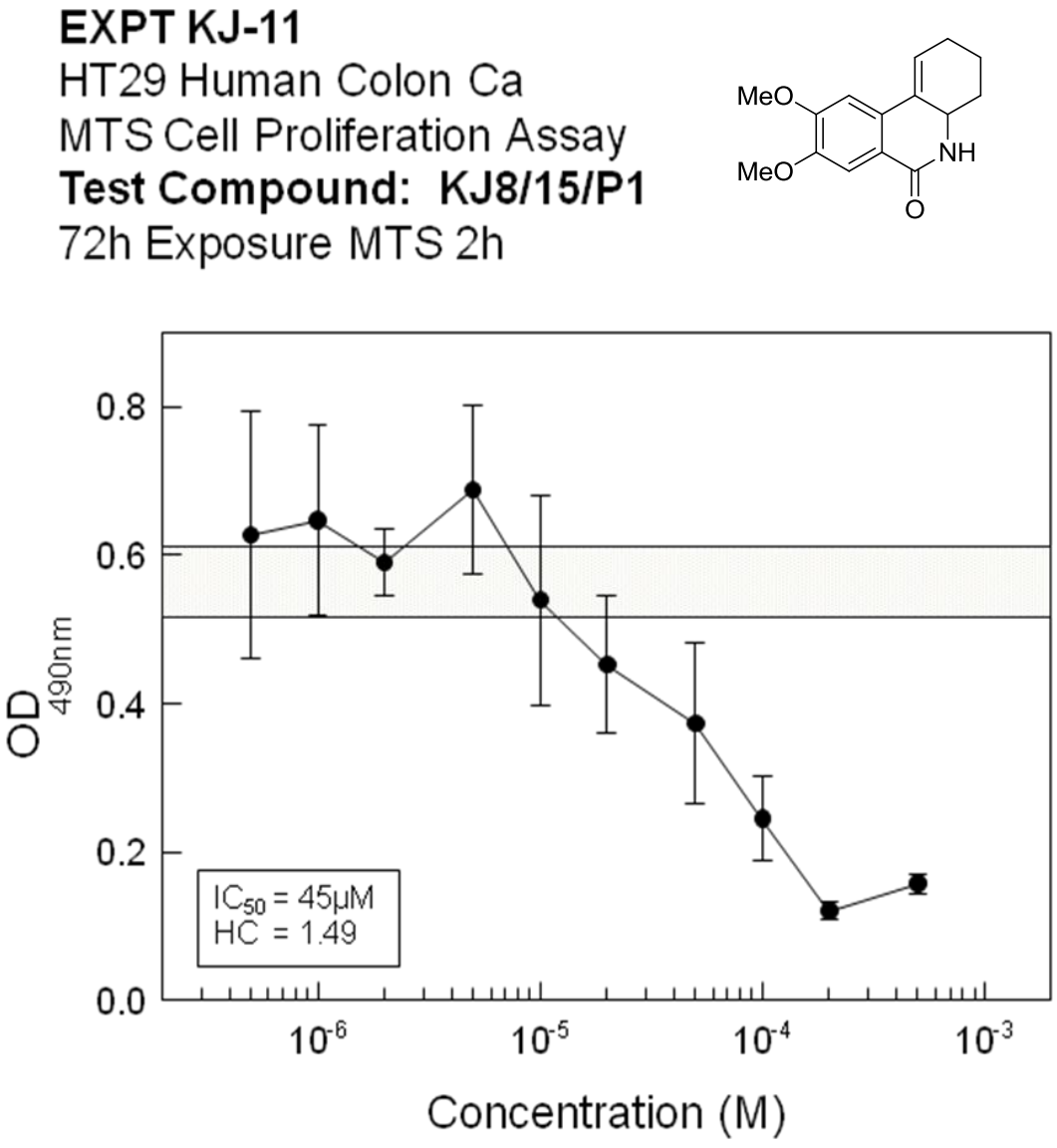
EXPT KJ-12
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ8/10/P
72h Exposure MTS 2h



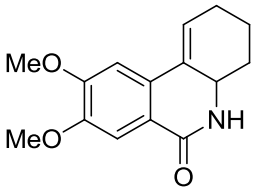


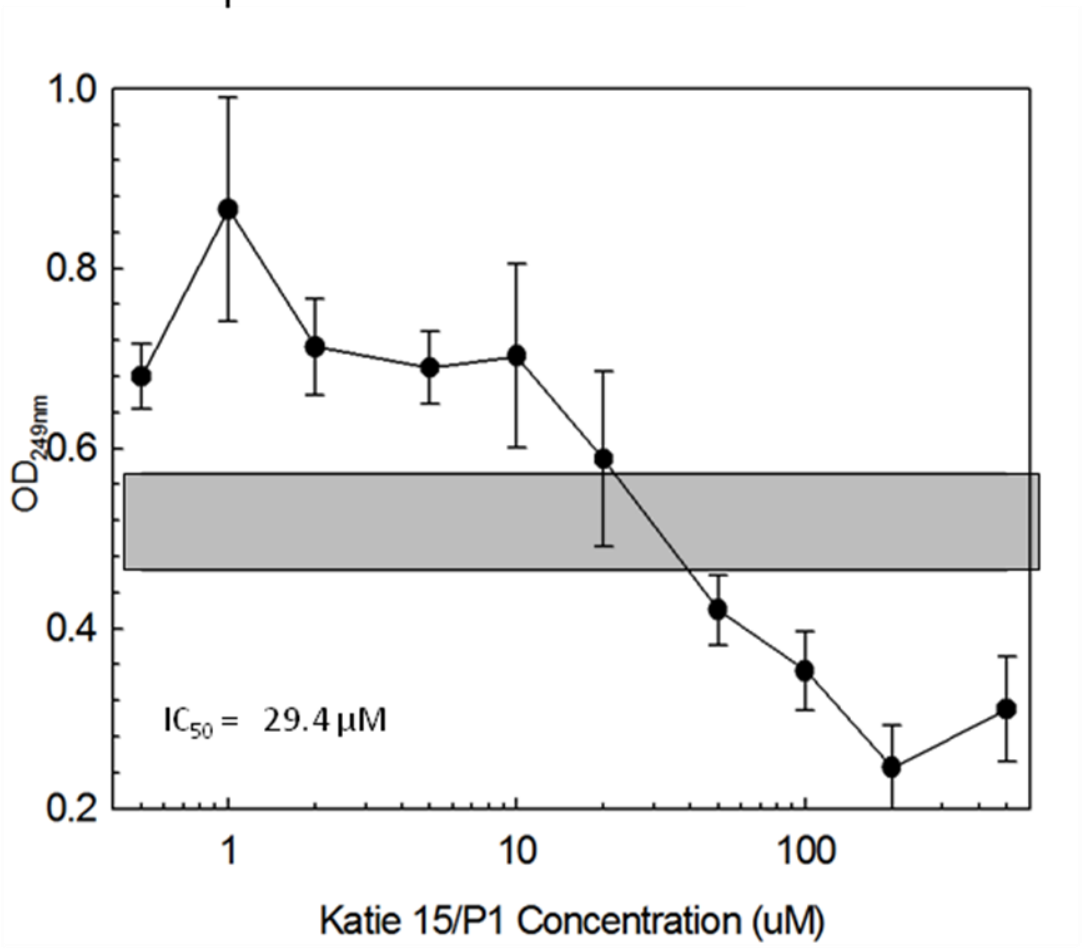
1% DMSO only
Points are means ± s.d
n = 4

8,9-Dimethoxy-3,4,4a,5-tetrahydrophenanthridin-6(2H)-one (239)



EXPT KJ-12
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ8/15/P1
72h Exposure MTS 2h

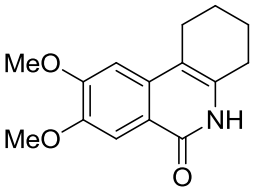


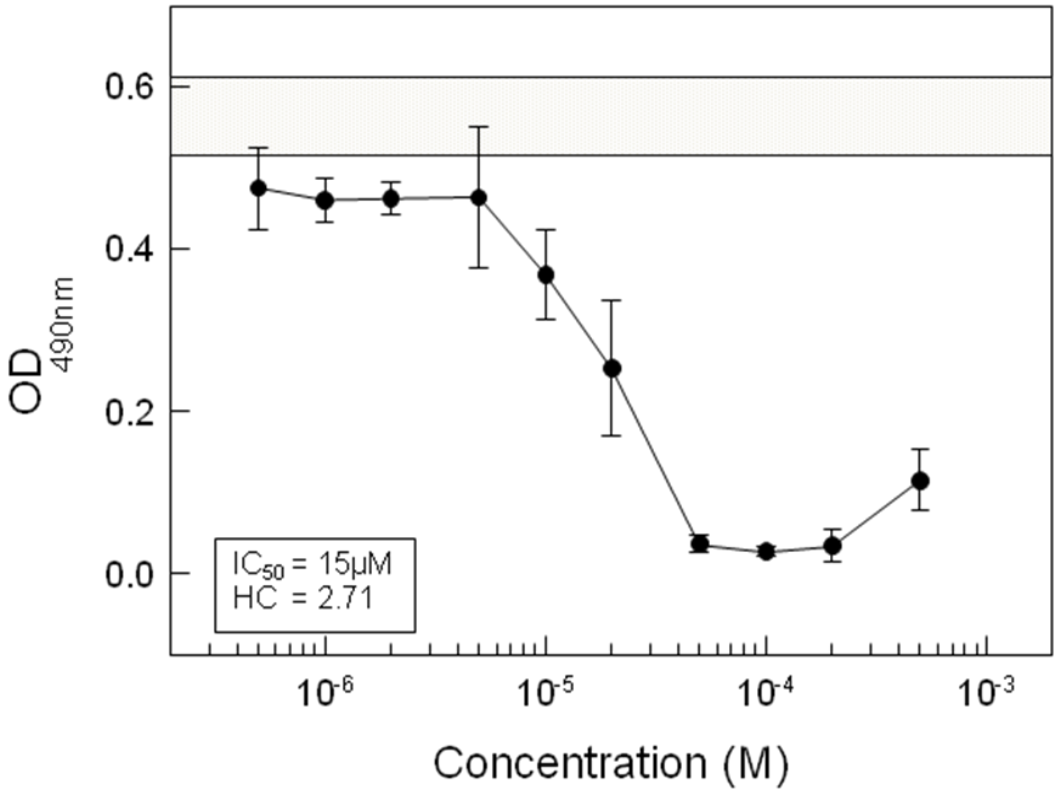


1% DMSO only
Points are means ± s.d
n = 4

8,9-Dimethoxy-1,2,3,4-tetrahydrophenanthridin-6(5H)-one (240)

EXPT KJ-11
HT29 Human Colon Ca
MTS Cell Proliferation Assay
Test Compound: KJ8/15/P2
72h Exposure MTS 2h





1% DMSO only
Points are means ± s.d
n = 4

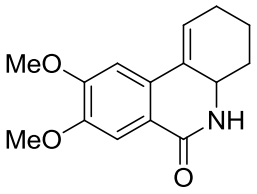
EXPT KJ-12

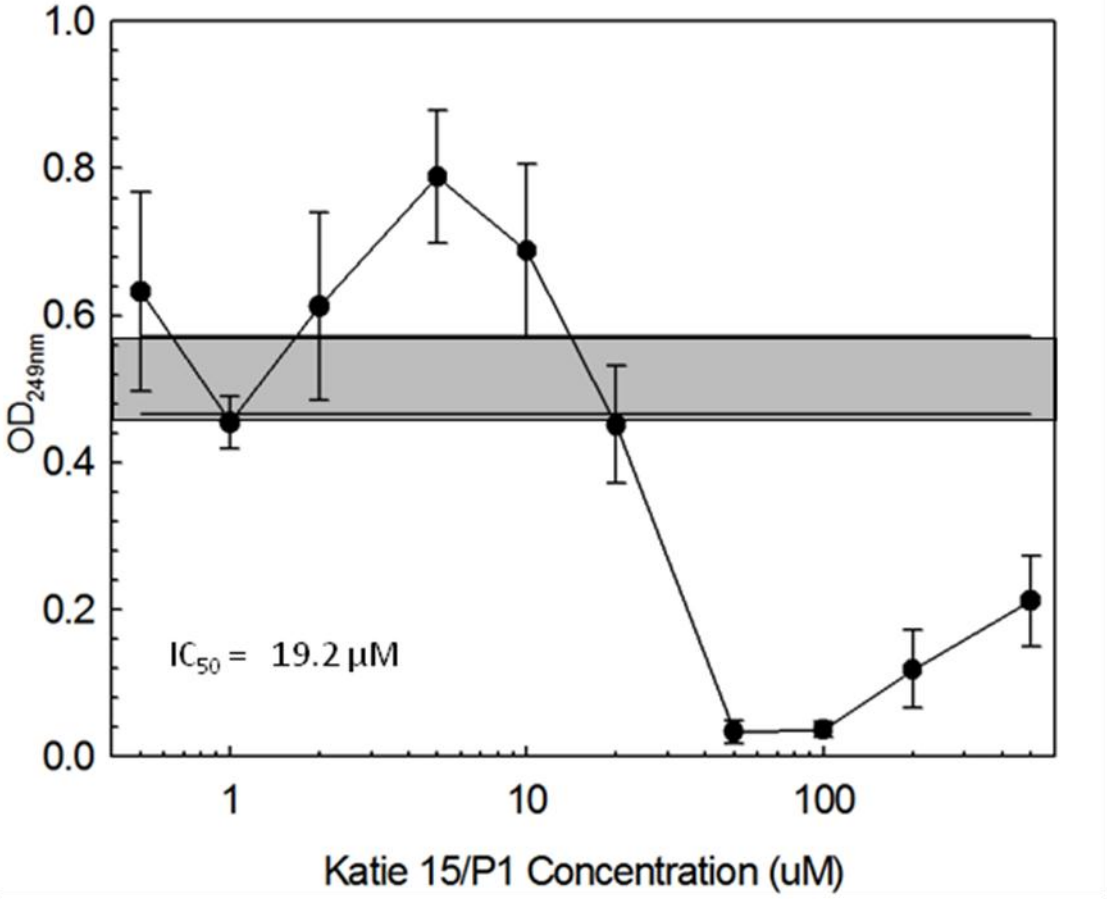
HT29 Human Colon Ca

MTS Cell Proliferation Assay

Test Compound: KJ8/15/P2

72h Exposure MTS 2h





1% DMSO only

Points are means ± s.d

n = 4

7.2. APPENDIX 2: CRYSTALLOGRAPHIC DATA

7.2.1. 8-(Difluoroboryloxy)-6,7-dimethoxy-3,4-dihydroisoquinolin-(2*H*)-one (148)

Table 1. Crystal data and structure refinement for 1.

Identification code	k08farm2
Empirical formula	C11 H12 B F2 N O4
Formula weight	271.03
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P21/c
Unit cell dimensions	a = 7.7930(1)Å □ = 90°
	b = 10.5440(2)Å □ = 102.540(1)°
	c = 14.7380(4)Å □ = 90°
Volume	1182.12(4) Å^3
Z	4
Density (calculated)	1.523 Mg/m^3
Absorption coefficient	0.133 mm^{-1}
F(000)	560
Crystal size	0.25 x 0.15 x 0.10 mm
Theta range for data collection	3.82 to 27.51 °.
Index ranges	-10<=h<=10; -13<=k<=13; -19<=l<=19
Reflections collected	21708
Independent reflections	2705 [R(int) = 0.0399]
Reflections observed (>2□)	2171
Data Completeness	0.996
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.98 and 0.94
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2705 / 0 / 175
Goodness-of-fit on F^2	1.013
Final R indices [I>2□(I)]	R1 = 0.0388 wR2 = 0.1003
R indices (all data)	R1 = 0.0531 wR2 = 0.1097
Largest diff. peak and hole	0.244 and -0.290 eÅ^{-3}

Notes: H…F interactions generate 1-D chains in the lattice.

Hydrogen bonds with H..A < r(A) + 2.000 Angstroms and <DHA > 110 deg.

D-H	d(D-H)	d(H..A)	<DHA	d(D..A)	A
N1-H1	0.880	2.002	156.91	2.833	F2 [-x, y+1/2, -z+3/2]
N1-H1	0.880	2.616	142.91	3.360	F1 [-x, y+1/2, -z+3/2]

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for 1.U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
F(1)	1729(1)	93(1)	6650(1)	43(1)
F(2)	-363(1)	-483(1)	7428(1)	36(1)
O(1)	4451(1)	-2210(1)	11188(1)	33(1)
O(2)	4219(1)	-2528(1)	9361(1)	29(1)
O(3)	2628(1)	-693(1)	8138(1)	28(1)
O(4)	1222(1)	1381(1)	7846(1)	30(1)
N(1)	1110(2)	2700(1)	9020(1)	28(1)
C(1)	2745(2)	-530(1)	9055(1)	22(1)
C(2)	3523(2)	-1458(1)	9681(1)	23(1)
C(3)	3629(2)	-1269(1)	10631(1)	24(1)
C(4)	2926(2)	-177(1)	10960(1)	25(1)
C(5)	2185(2)	755(1)	10341(1)	23(1)
C(6)	1364(2)	1947(1)	10625(1)	27(1)
C(7)	1573(2)	3061(1)	10006(1)	27(1)
C(8)	1454(2)	1572(1)	8737(1)	24(1)
C(9)	2114(2)	585(1)	9392(1)	21(1)
C(10)	4450(2)	-2145(2)	12162(1)	40(1)
C(11)	3102(2)	-3617(2)	9301(1)	43(1)
B(1)	1320(2)	47(2)	7507(1)	29(1)

Table 3. Bond lengths [Å] and angles [^{o}] for 1.

F(1)-B(1)	1.3700(18)	F(2)-B(1)	1.407(2)
O(1)-C(3)	1.3572(16)	O(1)-C(10)	1.4365(18)
O(2)-C(2)	1.3784(16)	O(2)-C(11)	1.4327(18)
O(3)-C(1)	1.3443(15)	O(3)-B(1)	1.4500(19)
O(4)-C(8)	1.3016(16)	O(4)-B(1)	1.4993(19)
N(1)-C(8)	1.3067(18)	N(1)-C(7)	1.4694(18)
N(1)-H(1)	0.8800	C(1)-C(2)	1.3905(18)
C(1)-C(9)	1.4062(18)	C(2)-C(3)	1.3991(19)
C(3)-C(4)	1.406(2)	C(4)-C(5)	1.3801(19)
C(4)-H(4)	0.9500	C(5)-C(9)	1.3992(18)
C(5)-C(6)	1.5097(18)	C(6)-C(7)	1.518(2)
C(6)-H(6A)	0.9900	C(6)-H(6B)	0.9900
C(7)-H(7A)	0.9900	C(7)-H(7B)	0.9900
C(8)-C(9)	1.4365(18)	C(10)-H(10A)	0.9800
C(10)-H(10B)	0.9800	C(10)-H(10C)	0.9800
C(11)-H(11A)	0.9800	C(11)-H(11B)	0.9800
C(11)-H(11C)	0.9800		
C(3)-O(1)-C(10)	117.83(12)	C(2)-O(2)-C(11)	113.47(10)
C(1)-O(3)-B(1)	117.40(11)	C(8)-O(4)-B(1)	118.40(11)
C(8)-N(1)-C(7)	121.88(11)	C(8)-N(1)-H(1)	119.1
C(7)-N(1)-H(1)	119.1	O(3)-C(1)-C(2)	120.07(12)

O(3)-C(1)-C(9)	120.62(12)	C(2)-C(1)-C(9)	119.30(12)
O(2)-C(2)-C(1)	119.75(12)	O(2)-C(2)-C(3)	121.11(11)
C(1)-C(2)-C(3)	119.11(12)	O(1)-C(3)-C(2)	114.77(12)
O(1)-C(3)-C(4)	123.93(12)	C(2)-C(3)-C(4)	121.30(12)
C(5)-C(4)-C(3)	119.55(12)	C(5)-C(4)-H(4)	120.2
C(3)-C(4)-H(4)	120.2	C(4)-C(5)-C(9)	119.35(12)
C(4)-C(5)-C(6)	123.39(12)	C(9)-C(5)-C(6)	117.21(12)
C(5)-C(6)-C(7)	111.69(11)	C(5)-C(6)-H(6A)	109.3
C(7)-C(6)-H(6A)	109.3	C(5)-C(6)-H(6B)	109.3
C(7)-C(6)-H(6B)	109.3	H(6A)-C(6)-H(6B)	107.9
N(1)-C(7)-C(6)	111.01(11)	N(1)-C(7)-H(7A)	109.4
C(6)-C(7)-H(7A)	109.4	N(1)-C(7)-H(7B)	109.4
C(6)-C(7)-H(7B)	109.4	H(7A)-C(7)-H(7B)	108.0
O(4)-C(8)-N(1)	118.05(12)	O(4)-C(8)-C(9)	121.07(12)
N(1)-C(8)-C(9)	120.86(12)	C(5)-C(9)-C(1)	121.29(12)
C(5)-C(9)-C(8)	120.61(12)	C(1)-C(9)-C(8)	118.05(12)
O(1)-C(10)-H(10A)	109.5	O(1)-C(10)-H(10B)	109.5
H(10A)-C(10)-H(10B)	109.5	O(1)-C(10)-H(10C)	109.5
H(10A)-C(10)-H(10C)	109.5	H(10B)-C(10)-H(10C)	109.5
O(2)-C(11)-H(11A)	109.5	O(2)-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11B)	109.5	O(2)-C(11)-H(11C)	109.5
H(11A)-C(11)-H(11C)	109.5	H(11B)-C(11)-H(11C)	109.5
F(1)-B(1)-F(2)	109.68(12)	F(1)-B(1)-O(3)	109.82(13)
F(2)-B(1)-O(3)	110.60(12)	F(1)-B(1)-O(4)	108.23(12)
F(2)-B(1)-O(4)	106.66(12)	O(3)-B(1)-O(4)	111.76(11)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2$ x 10^3) for 1. The anisotropic displacement
factor exponent takes the form: -2 gpi^2 [h^2 a^{*2} U11 + ... + 2 h k a* b* U

Atom	U11	U22	U33	U23	U13	U12
F(1)	67(1)	38(1)	23(1)	2(1)	12(1)	6(1)
F(2)	37(1)	32(1)	36(1)	-7(1)	-1(1)	-1(1)
O(1)	35(1)	30(1)	30(1)	11(1)	3(1)	3(1)
O(2)	28(1)	22(1)	38(1)	1(1)	9(1)	2(1)
O(3)	35(1)	26(1)	21(1)	-2(1)	6(1)	3(1)
O(4)	43(1)	24(1)	22(1)	1(1)	1(1)	2(1)
N(1)	32(1)	22(1)	26(1)	1(1)	-1(1)	4(1)
C(1)	21(1)	24(1)	22(1)	-1(1)	6(1)	-2(1)
C(2)	19(1)	22(1)	29(1)	0(1)	6(1)	0(1)
C(3)	19(1)	25(1)	27(1)	6(1)	3(1)	-3(1)
C(4)	24(1)	30(1)	23(1)	2(1)	6(1)	-4(1)
C(5)	19(1)	25(1)	25(1)	-1(1)	5(1)	-4(1)

C(6)	26(1)	29(1)	28(1)	-3(1)	8(1)	0(1)
C(7)	28(1)	25(1)	28(1)	-5(1)	3(1)	1(1)
C(8)	23(1)	24(1)	24(1)	-1(1)	2(1)	-1(1)
C(9)	19(1)	22(1)	23(1)	0(1)	4(1)	-2(1)
C(10)	44(1)	46(1)	29(1)	16(1)	5(1)	-1(1)
C(11)	46(1)	26(1)	61(1)	-8(1)	18(1)	-5(1)
B(1)	40(1)	25(1)	22(1)	-1(1)	3(1)	2(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 1.

Atom	x	y	z	U(eq)
H(1)	585	3258	8608	33
H(4)	2960	-82	11605	30
H(6A)	1924	2155	11277	33
H(6B)	98	1796	10592	33
H(7A)	807	3766	10119	33
H(7B)	2806	3362	10163	33
H(10A)	5103	-1392	12433	60
H(10B)	5011	-2907	12474	60
H(10C)	3237	-2092	12242	60
H(11A)	2854	-3793	9913	65
H(11B)	3690	-4351	9096	65
H(11C)	1996	-3453	8853	65

Table 6. Dihedral angles [^{o}] for 1.

Atom1 - Atom2 - Atom3 - Atom4	Dihedral
B(1) - O(3) - C(1) - C(2)	159.26(12)
B(1) - O(3) - C(1) - C(9)	-21.87(17)
C(11) - O(2) - C(2) - C(1)	-101.17(15)
C(11) - O(2) - C(2) - C(3)	80.74(16)
O(3) - C(1) - C(2) - O(2)	1.91(18)
C(9) - C(1) - C(2) - O(2)	-176.97(11)
O(3) - C(1) - C(2) - C(3)	-179.96(11)
C(9) - C(1) - C(2) - C(3)	1.16(18)
C(10) - O(1) - C(3) - C(2)	-173.73(12)
C(10) - O(1) - C(3) - C(4)	6.28(19)
O(2) - C(2) - C(3) - O(1)	-0.22(17)
C(1) - C(2) - C(3) - O(1)	-178.32(11)
O(2) - C(2) - C(3) - C(4)	179.78(11)
C(1) - C(2) - C(3) - C(4)	1.67(19)
O(1) - C(3) - C(4) - C(5)	177.04(12)
C(2) - C(3) - C(4) - C(5)	-2.95(19)
C(3) - C(4) - C(5) - C(9)	1.32(19)
C(3) - C(4) - C(5) - C(6)	178.70(11)

C(4) - C(5) - C(6) - C(7)	148.52(12)
C(9) - C(5) - C(6) - C(7)	-34.05(16)
C(8) - N(1) - C(7) - C(6)	-35.53(17)
C(5) - C(6) - C(7) - N(1)	46.70(15)
B(1) - O(4) - C(8) - N(1)	-169.95(13)
B(1) - O(4) - C(8) - C(9)	11.75(18)
C(7) - N(1) - C(8) - O(4)	-170.82(12)
C(7) - N(1) - C(8) - C(9)	7.49(19)
C(4) - C(5) - C(9) - C(1)	1.52(18)
C(6) - C(5) - C(9) - C(1)	-176.02(11)
C(4) - C(5) - C(9) - C(8)	-176.01(12)
C(6) - C(5) - C(9) - C(8)	6.46(17)
O(3) - C(1) - C(9) - C(5)	178.34(11)
C(2) - C(1) - C(9) - C(5)	-2.78(18)
O(3) - C(1) - C(9) - C(8)	-4.07(18)
C(2) - C(1) - C(9) - C(8)	174.80(11)
O(4) - C(8) - C(9) - C(5)	-173.27(12)
N(1) - C(8) - C(9) - C(5)	8.47(19)
O(4) - C(8) - C(9) - C(1)	9.13(18)
N(1) - C(8) - C(9) - C(1)	-169.13(12)
C(1) - O(3) - B(1) - F(1)	160.54(11)
C(1) - O(3) - B(1) - F(2)	-78.27(14)
C(1) - O(3) - B(1) - O(4)	40.40(17)
C(8) - O(4) - B(1) - F(1)	-156.70(12)
C(8) - O(4) - B(1) - F(2)	85.35(14)
C(8) - O(4) - B(1) - O(3)	-35.64(18)

7.2.2. 2,3,4,9-Tetrahydro-β-carbolin-1-one (153)

Table 1. Crystal data and structure refinement for 1.

Identification code	h08farm1
Empirical formula	C23 H21 Cl3 N4 O2
Formula weight	491.79
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P21/c
Unit cell dimensions	a = 12.5260(2)Å □ = 90°
	b = 12.9790(2)Å □ = 107.493(1)°
	c = 15.0540(2)Å □ = 90°
Volume	2334.22(6) $Å^3$
Z	4
Density (calculated)	1.399 Mg/m^3
Absorption coefficient	0.421 mm^{-1}
F(000)	1016
Crystal size	0.35 x 0.18 x 0.13 mm
Theta range for data collection	3.65 to 27.50°
Index ranges	-16<=h<=16; -16<=k<=16; -19<=l<=19

Reflections collected	33937
Independent reflections	5345 [R(int) = 0.0743]
Reflections observed (>2□)	3659
Data Completeness	0.996
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.95 and 0.88
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5345 / 0 / 317
Goodness-of-fit on F^2	1.036
Final R indices [I>2□(I)]	R1 = 0.0667 wR2 = 0.1741
R indices (all data)	R1 = 0.1011 wR2 = 0.2000
Largest diff. peak and hole	0.604 and -0.692 eÅ^{-3}

Notes: The asymmetric unti contains 2 molecules and 1 molecule of solvent of recrystallization ($CHCl_3$). The latter exhibited disorder of the chlorines which was modeled as a 65:35 ratio. The gross structure consists of hydrogen-bonded tapes.

Hydrogen bonds with H..A < r(A) + 2.000 Angstroms and <DHA > 110 deg.

D-H	d(D-H)	d(H..A)	<DHA	d(D..A)	A
N1-H1	0.880	1.963	169.68	2.834	O1A [x, -y+1/2, z+1/2]
N2-H2	0.880	1.967	170.12	2.838	O1A
N1A-H1A	0.880	2.056	161.07	2.903	O1
N2A-H2A	0.880	2.029	172.88	2.904	O1 [x, -y+1/2, z-1/2]

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for 1.U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
Cl(1)	3009(4)	5314(2)	4172(2)	159(1)
Cl(2)	4244(3)	5379(2)	2868(2)	119(1)
Cl(3)	2224(1)	4260(1)	2450(2)	87(1)
O(1)	4739(1)	2499(1)	3174(1)	31(1)
N(1)	3078(2)	1770(2)	4042(1)	28(1)
N(2)	3599(2)	1924(2)	1788(1)	31(1)
C(1)	3857(2)	2062(2)	2705(2)	27(1)
C(2)	2679(2)	1260(2)	1273(2)	38(1)
C(3)	1620(2)	1433(2)	1552(2)	38(1)
C(4)	1932(2)	1471(2)	2592(2)	30(1)

C(5)	1295(2)	1362(2)	3229(2)	29(1)
C(6)	165(2)	1130(2)	3135(2)	36(1)
C(7)	-160(2)	1070(2)	3929(2)	41(1)
C(8)	601(2)	1226(2)	4812(2)	40(1)
C(9)	1711(2)	1458(2)	4933(2)	33(1)
C(10)	2041(2)	1538(2)	4126(2)	28(1)
C(11)	2997(2)	1722(2)	3112(2)	27(1)
C(33)	3523(4)	4638(3)	3382(3)	70(1)
Cl(1A)	4170(5)	5491(5)	4401(6)	194(4)
Cl(2A)	3937(7)	4980(6)	2408(4)	165(3)
Cl(3A)	2323(2)	4337(3)	3338(4)	106(1)
O(1A)	4851(1)	2742(2)	662(1)	35(1)
N(1A)	6497(2)	3276(2)	2463(1)	30(1)
N(2A)	6118(2)	3281(2)	-42(1)	34(1)
C(1A)	5793(2)	3115(2)	718(2)	30(1)
C(2A)	7091(2)	3921(2)	-24(2)	36(1)
C(3A)	8100(2)	3676(2)	814(2)	34(1)
C(4A)	7727(2)	3585(2)	1663(2)	29(1)
C(5A)	8316(2)	3640(2)	2630(2)	28(1)
C(6A)	9434(2)	3831(2)	3143(2)	34(1)
C(7A)	9722(2)	3846(2)	4100(2)	38(1)
C(8A)	8915(2)	3675(2)	4559(2)	37(1)
C(9A)	7810(2)	3472(2)	4079(2)	33(1)
C(10A)	7519(2)	3447(2)	3108(2)	29(1)
C(11A)	6635(2)	3355(2)	1592(2)	29(1)

Table 3. Bond lengths [Å] and angles [^{o}] for 1.

Cl(1)-C(33)	1.749(4)	Cl(2)-C(33)	1.661(4)
Cl(3)-C(33)	1.866(5)	O(1)-C(1)	1.254(3)
N(1)-C(11)	1.374(3)	N(1)-C(10)	1.375(3)
N(1)-H(1)	0.8800	N(2)-C(1)	1.332(3)
N(2)-C(2)	1.461(3)	N(2)-H(2)	0.8800
C(1)-C(11)	1.459(3)	C(2)-C(3)	1.523(4)
C(2)-H(2C)	0.9900	C(2)-H(2B)	0.9900
C(3)-C(4)	1.497(3)	C(3)-H(3A)	0.9900
C(3)-H(3B)	0.9900	C(4)-C(11)	1.367(3)
C(4)-C(5)	1.427(3)	C(5)-C(10)	1.411(3)
C(5)-C(6)	1.412(3)	C(6)-C(7)	1.374(4)
C(6)-H(6)	0.9500	C(7)-C(8)	1.398(4)
C(7)-H(7)	0.9500	C(8)-C(9)	1.380(4)
C(8)-H(8)	0.9500	C(9)-C(10)	1.400(3)
C(9)-H(9)	0.9500	C(33)-Cl(3A)	1.535(5)
C(33)-Cl(2A)	1.754(7)	C(33)-Cl(1A)	1.868(6)
C(33)-H(33)	1.0000	O(1A)-C(1A)	1.255(3)
N(1A)-C(10A)	1.373(3)	N(1A)-C(11A)	1.377(3)
N(1A)-H(1A)	0.8800	N(2A)-C(1A)	1.341(3)
N(2A)-C(2A)	1.469(3)	N(2A)-H(2A)	0.8800
C(1A)-C(11A)	1.452(3)	C(2A)-C(3A)	1.526(4)
C(2A)-H(2A1)	0.9900	C(2A)-H(2A2)	0.9900

C(3A)-C(4A)	1.492(3)	C(3A)-H(3A1)	0.9900
C(3A)-H(3A2)	0.9900	C(4A)-C(11A)	1.372(3)
C(4A)-C(5A)	1.421(3)	C(5A)-C(6A)	1.404(3)
C(5A)-C(10A)	1.417(3)	C(6A)-C(7A)	1.376(4)
C(6A)-H(6A)	0.9500	C(7A)-C(8A)	1.403(4)
C(7A)-H(7A)	0.9500	C(8A)-C(9A)	1.380(4)
C(8A)-H(8A)	0.9500	C(9A)-C(10A)	1.397(3)
C(9A)-H(9A)	0.9500		
C(11)-N(1)-C(10)	107.55(19)	C(11)-N(1)-H(1)	126.2
C(10)-N(1)-H(1)	126.2	C(1)-N(2)-C(2)	122.42(19)
C(1)-N(2)-H(2)	118.8	C(2)-N(2)-H(2)	118.8
O(1)-C(1)-N(2)	122.9(2)	O(1)-C(1)-C(11)	122.5(2)
N(2)-C(1)-C(11)	114.5(2)	N(2)-C(2)-C(3)	112.4(2)
N(2)-C(2)-H(2C)	109.1	C(3)-C(2)-H(2C)	109.1
N(2)-C(2)-H(2B)	109.1	C(3)-C(2)-H(2B)	109.1
H(2C)-C(2)-H(2B)	107.9	C(4)-C(3)-C(2)	108.5(2)
C(4)-C(3)-H(3A)	110.0	C(2)-C(3)-H(3A)	110.0
C(4)-C(3)-H(3B)	110.0	C(2)-C(3)-H(3B)	110.0
H(3A)-C(3)-H(3B)	108.4	C(11)-C(4)-C(5)	106.6(2)
C(11)-C(4)-C(3)	120.6(2)	C(5)-C(4)-C(3)	132.6(2)
C(10)-C(5)-C(6)	119.1(2)	C(10)-C(5)-C(4)	106.4(2)
C(6)-C(5)-C(4)	134.4(2)	C(7)-C(6)-C(5)	118.3(2)
C(7)-C(6)-H(6)	120.9	C(5)-C(6)-H(6)	120.9
C(6)-C(7)-C(8)	121.6(2)	C(6)-C(7)-H(7)	119.2
C(8)-C(7)-H(7)	119.2	C(9)-C(8)-C(7)	121.9(2)
C(9)-C(8)-H(8)	119.1	C(7)-C(8)-H(8)	119.1
C(8)-C(9)-C(10)	116.8(2)	C(8)-C(9)-H(9)	121.6
C(10)-C(9)-H(9)	121.6	N(1)-C(10)-C(9)	129.0(2)
N(1)-C(10)-C(5)	108.66(19)	C(9)-C(10)-C(5)	122.3(2)
C(4)-C(11)-N(1)	110.72(19)	C(4)-C(11)-C(1)	123.2(2)
N(1)-C(11)-C(1)	125.2(2)	Cl(3A)-C(33)-Cl(2)	142.2(4)
Cl(3A)-C(33)-Cl(1)	66.5(3)	Cl(2)-C(33)-Cl(1)	112.9(3)
Cl(3A)-C(33)-Cl(2A)	124.1(5)	Cl(2)-C(33)-Cl(2A)	28.9(3)
Cl(1)-C(33)-Cl(2A)	134.7(4)	Cl(3A)-C(33)-Cl(3)	43.9(2)
Cl(2)-C(33)-Cl(3)	106.0(3)	Cl(1)-C(33)-Cl(3)	103.1(3)
Cl(2A)-C(33)-Cl(3)	81.3(4)	Cl(3A)-C(33)-Cl(1A)	111.3(4)
Cl(2)-C(33)-Cl(1A)	82.9(4)	Cl(1)-C(33)-Cl(1A)	45.7(2)
Cl(2A)-C(33)-Cl(1A)	111.9(5)	Cl(3)-C(33)-Cl(1A)	146.9(3)
Cl(3A)-C(33)-H(33)	102.7	Cl(2)-C(33)-H(33)	111.5
Cl(1)-C(33)-H(33)	111.5	Cl(2A)-C(33)-H(33)	108.3
Cl(3)-C(33)-H(33)	111.5	Cl(1A)-C(33)-H(33)	93.6
C(10A)-N(1A)-C(11A)	107.66(19)	C(10A)-N(1A)-H(1A)	126.2
C(11A)-N(1A)-H(1A)	126.2	C(1A)-N(2A)-C(2A)	122.5(2)
C(1A)-N(2A)-H(2A)	118.7	C(2A)-N(2A)-H(2A)	118.7
O(1A)-C(1A)-N(2A)	121.7(2)	O(1A)-C(1A)-C(11A)	123.7(2)

N(2A)-C(1A)-C(11A)	114.5(2)	N(2A)-C(2A)-C(3A)	112.0(2)
N(2A)-C(2A)-H(2A1)	109.2	C(3A)-C(2A)-H(2A1)	109.2
N(2A)-C(2A)-H(2A2)	109.2	C(3A)-C(2A)-H(2A2)	109.2
H(2A1)-C(2A)-H(2A2)	107.9	C(4A)-C(3A)-C(2A)	109.23(19)
C(4A)-C(3A)-H(3A1)	109.8	C(2A)-C(3A)-H(3A1)	109.8
C(4A)-C(3A)-H(3A2)	109.8	C(2A)-C(3A)-H(3A2)	109.8
H(3A1)-C(3A)-H(3A2)	108.3	C(11A)-C(4A)-C(5A)	106.8(2)
C(11A)-C(4A)-C(3A)	120.8(2)	C(5A)-C(4A)-C(3A)	132.4(2)
C(6A)-C(5A)-C(10A)	119.3(2)	C(6A)-C(5A)-C(4A)	134.2(2)
C(10A)-C(5A)-C(4A)	106.5(2)	C(7A)-C(6A)-C(5A)	118.9(2)
C(7A)-C(6A)-H(6A)	120.6	C(5A)-C(6A)-H(6A)	120.6
C(6A)-C(7A)-C(8A)	120.8(2)	C(6A)-C(7A)-H(7A)	119.6
C(8A)-C(7A)-H(7A)	119.6	C(9A)-C(8A)-C(7A)	122.0(2)
C(9A)-C(8A)-H(8A)	119.0	C(7A)-C(8A)-H(8A)	119.0
C(8A)-C(9A)-C(10A)	117.2(2)	C(8A)-C(9A)-H(9A)	121.4
C(10A)-C(9A)-H(9A)	121.4	N(1A)-C(10A)-C(9A)	129.7(2)
N(1A)-C(10A)-C(5A)	108.6(2)	C(9A)-C(10A)-C(5A)	121.7(2)
C(4A)-C(11A)-N(1A)	110.5(2)	C(4A)-C(11A)-C(1A)	123.6(2)
N(1A)-C(11A)-C(1A)	125.6(2)		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2$ x 10^3) for 1. The anisotropic displacement
factor exponent takes the form: -2 gpi^2 [h^2 a^{*2} U11 + ... + 2 h k a* b* U

Atom	U11	U22	U33	U23	U13	U12
Cl(1)	275(4)	125(2)	122(2)	-27(2)	129(3)	33(2)
Cl(2)	143(2)	110(2)	137(2)	-23(2)	93(2)	-69(2)
Cl(3)	58(1)	69(1)	126(2)	-12(1)	14(1)	12(1)
O(1)	26(1)	45(1)	24(1)	2(1)	9(1)	-5(1)
N(1)	24(1)	38(1)	22(1)	0(1)	8(1)	-3(1)
N(2)	34(1)	37(1)	23(1)	-1(1)	11(1)	-8(1)
C(1)	26(1)	29(1)	25(1)	3(1)	9(1)	1(1)
C(2)	45(2)	45(2)	25(1)	-4(1)	10(1)	-12(1)

C(3)	37(1)	46(2)	27(1)	6(1)	4(1)	-14(1)
C(4)	32(1)	28(1)	28(1)	3(1)	8(1)	-5(1)
C(5)	26(1)	27(1)	34(1)	3(1)	9(1)	-3(1)
C(6)	28(1)	32(1)	46(2)	1(1)	10(1)	-4(1)
C(7)	31(1)	35(1)	64(2)	-2(1)	24(1)	-3(1)
C(8)	43(2)	36(1)	50(2)	-5(1)	31(1)	-4(1)
C(9)	38(1)	33(1)	35(1)	-2(1)	20(1)	-1(1)
C(10)	29(1)	27(1)	32(1)	-1(1)	16(1)	-2(1)
C(11)	28(1)	30(1)	24(1)	1(1)	10(1)	-3(1)
C(33)	90(3)	50(2)	89(3)	-8(2)	53(2)	-6(2)
Cl(1A)	114(4)	126(4)	299(9)	-129(5)	-3(4)	11(3)
Cl(2A)	244(8)	144(6)	117(4)	63(4)	68(5)	56(5)
Cl(3A)	36(1)	79(2)	191(4)	29(3)	18(2)	-4(1)
O(1A)	25(1)	56(1)	25(1)	3(1)	7(1)	-7(1)
N(1A)	24(1)	44(1)	23(1)	-1(1)	8(1)	-4(1)
N(2A)	31(1)	48(1)	25(1)	-6(1)	12(1)	-11(1)
C(1A)	26(1)	38(1)	26(1)	-1(1)	10(1)	-2(1)
C(2A)	36(1)	49(2)	30(1)	-3(1)	17(1)	-11(1)
C(3A)	29(1)	45(2)	34(1)	-9(1)	17(1)	-9(1)
C(4A)	28(1)	31(1)	29(1)	-4(1)	11(1)	-2(1)
C(5A)	28(1)	26(1)	30(1)	-2(1)	9(1)	-1(1)
C(6A)	28(1)	33(1)	40(1)	1(1)	8(1)	-2(1)
C(7A)	32(1)	36(1)	39(1)	2(1)	0(1)	-4(1)
C(8A)	40(1)	38(1)	27(1)	2(1)	0(1)	-4(1)
C(9A)	36(1)	35(1)	27(1)	2(1)	8(1)	-2(1)
C(10A)	26(1)	31(1)	28(1)	-1(1)	7(1)	-1(1)
C(11A)	25(1)	39(1)	24(1)	-2(1)	10(1)	-3(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 1.

Atom	x	y	z	U(eq)
H(1)	3682	1922	4500	34
H(2)	3997	2244	1480	37
H(2C)	2911	530	1388	46
H(2B)	2515	1394	598	46
H(3A)	1261	2089	1284	45
H(3B)	1083	866	1312	45
H(6)	-358	1018	2539	43
H(7)	-918	920	3875	49
H(8)	346	1171	5344	47
H(9)	2226	1557	5535	40
H(33)	3965	4020	3679	84
H(1A)	5866	3140	2584	36
H(2A)	5734	2994	-571	40
H(2A1)	6891	4656	-2	44
H(2A2)	7293	3807	-603	44
H(3A1)	8448	3021	706	41
H(3A2)	8665	4230	901	41

H(6A)	9983	3948	2835	41
H(7A)	10476	3974	4455	45
H(8A)	9135	3698	5220	44
H(9A)	7270	3355	4396	40